UNITED STATES DISTRICT COURT
FOR THE
DISTRICT OF MASSACHUSETTS

JOHN HANCOCK LIFE INSURANCE COMPANY, JOHN HANCOCK VARIABLE LIFE INSURANCE COMPANY, and MANULIFE INSURANCE COMPANY (f/k/a INVESTORS PARTNER LIFE INSURANCE COMPANY), Plaintiffs, v. ABBOTT LABORATORIES, Defendant.	CIVIL ACTION NO. 05-11150-DPW

AFFIDAVIT OF LYNN C. KLOTZ, PH.D.

I, Lynn C. Klotz, hereby state under oath that:

1. My name is Lynn Charles Klotz. I currently reside at 5 Duley Street, Gloucester, Massachusetts.

My Background

2. I work as an independent consultant and advisor in the fields of biotechnology and biosecurity. I was retained by plaintiff John Hancock Life Insurance Company ("John Hancock" of "Hancock") in 2000 to assist Hancock and its affiliates in evaluating a portfolio of pharmaceutical compounds that then were under development by defendant Abbott Laboratories ("Abbott") in connection with a potential investment in those compounds by

Hancock. I have been called to testify in this action concerning my consulting work for John Hancock with respect to that investment. This affidavit sets forth my direct trial testimony.

3. A true and accurate copy of my Curriculum Vitae as of the time I was employed by John Hancock is attached hereto as PLs' KS. A brief summary of my educational and employment background is as follows.

4. I graduated from Princeton University in 1965 with a Bachelors Degree in Mathematics. I subsequently obtained a Ph.D. in Chemistry from the University of California, San Diego in 1971.

5. After graduate school, I joined the faculty of Harvard University as an assistant professor in Harvard's Biochemistry and Molecular Biology Department. In 1975, I was promoted to the position of associate professor. In 1979, I left Harvard to lecture in physical biochemistry for the Department of Biochemical Sciences at Princeton University.

6. In 1981, I became Vice President of Scientific Operations of BioTechnica International, Inc. ("BioTechnica"), a biotechnology company engaged in the discovery of antibiotics and other products through the use of bacterial genetic engineering. My responsibilities at BioTechnica focused primarily on new business development and strategic planning. I eventually also served as Vice Chairman of the Board of BioTechnica Diagnostics, a joint venture between BioTechnica and Forsyth Dental Research Institution of Boston, that developed DNA probes for the early detection and to guide treatment of periodontal disease.

7. In 1990, I became the managing partner of the Devonshire Biotechnology Group ("Devonshire"), an independent consulting organization within Devonshire Partners, Inc., that provided technical, strategic and managerial advice and assistance to public and private entities

in the biotechnology field. I eventually left Devonshire in approximately 1992 to lecture and consult in the same field on my own, and have been doing so ever since that time.

8. One pharmaceutical company for which I did a substantial amount of consulting work was Codon Pharmaceuticals ("Codon"), a wholly-owned subsidiary of Oncor, Inc. Codon was focused on the field of human gene repair. As a consultant to Codon, I provided assistance in the areas of technical strategy, pharmacokinetics, pharmacology, market and competition analyses for oligonucleotides and nucleoside-analog drugs that Codon was developing or seeking to develop. I also served on Codon's Scientific Advisory Board.

9. On various occasions since the mid-1990s, I have lectured and taught courses on the topics of biotechnology, drug discovery and drug development as part of Harvard University's Division of Continuing Education and Summer Executive Program under the Division of Continuing Education. My work in this regard and for Codon has required me to study and become generally knowledgeable about, among other things, pharmaceutical development practices, various types of pharmaceutical compounds, and the operations of the pharmaceutical industry as a whole.

My Prior Consulting Work for John Hancock

10. The Abbott assignment in 2000 was not the first time that I served as a consultant to John Hancock. Prior to 2000, I was retained by Hancock to help evaluate certain other actual or potential investments in the biotechnology and pharmaceutical fields.

11. For example, in 1998, I was retained by John Hancock to help evaluate the status of an existing Hancock investment in another drug company (Idun Pharmaceuticals, Inc.) that was engaged in cancer research involving "apoptosis" (*i.e.*, programmed cell death). I was asked by Stephen Blewitt at John Hancock to evaluate the status of various types of cancer

research, learn about cutting-edge therapies, and provide feedback to Hancock regarding which therapies looked promising and which did not.

12. I subsequently reviewed, at John Hancock's request, a proposed investment that Hancock was considering making in SangStat Medical Corp. ("SangStat"), a pharmaceutical company that developed and marketed immunosuppression treatments for organ transplant patients. I recommended that John Hancock not proceed with that investment because of concerns about certain litigation that was pending against SangStat. I recall that Hancock heeded my advice.

13. In or about May 1999, I entered into a retention agreement with John Hancock whereby I agreed to provide consulting services to Hancock "from time to time" as needed. A true and accurate copy of that agreement is attached hereto as PLs' RR. Under the terms of that agreement, John Hancock agreed to compensate for my consulting services at the rate of $200 per hour, plus expenses.

My Consulting Work Concerning John Hancock's Proposed Deal with Abbott

14. My next consulting assignment for John Hancock concerned Hancock's proposed pharmaceutical investment deal with Abbott. I first was asked by Mr. Blewitt to consult on that matter sometime in or around the spring of 2000. As Mr. Blewitt explained to me at that time, John Hancock was considering making a significant investment in a portfolio or "basket" of pharmaceutical compounds that then were being developed by Abbott.

15. My assignment was to review the descriptions and data regarding those compounds that was provided to Hancock by Abbott, and then attempt to verify the accuracy of Abbott's information using literature searches and other publicly-available sources, as well as discussions with independent researchers in the field. My goal was to determine, to the best

of my ability, whether the information supplied to John Hancock by Abbott was consistent with what was available elsewhere.

16. I was not retained by John Hancock to comprehensively examine the science behind the Abbott compounds, nor was I retained to provide any modeling or analysis of the financial side of the proposed deal.

17. I agreed to assist John Hancock in evaluating the proposed basket of Abbott compounds as requested. Most of my research and analysis was conducted in the months of June and July 2000. The starting point for my work was a series of draft "Descriptive Memoranda" that Abbott had prepared and supplied to John Hancock for each of the proposed compounds. I reviewed copies of the draft Descriptive Memoranda for a total of eight compounds: five compounds (ABT-627, A-245751 [a/k/a ABT-751], ABT-518 [a/k/a the "MMPI Program"], the "FTI Program" and "Urokinase Inhibitors") that were being developed to treat cancer; one compound (ABT-594) that was being developed to treat pain; one compound (ABT-980) that was being developed to treat benign prostatic hyperplasia (*i.e.*, blockage of the urinary tract); and one anti-infective or antibiotic (ABT-773). The majority of the compounds were in various stages of clinical trials at the time of my analysis, while at least two of the compounds still were in preclinical development.

18. Although the format of Abbott's individual Descriptive Memoranda varied somewhat, the ones I reviewed contained, in part: (a) a basic overview of the subject compound that described, among other things, the technical merits and development status of the compound, including the status and/or results of any clinical trials; (b) a discussion of the expected market for the compound, including the specific indications (*i.e.*, conditions or disease states) for which the compound was being developed by Abbott and estimates of the

size of the U.S. and ex-U.S. commercial markets for each indication; (c) a description of the nature and severity of any known or suspected side effects and other important "considerations"; (d) an identification of any actual or potential competing products; and (e) a discussion of Abbott's current and future development plans for the compound. Each Descriptive Memorandum was clearly marked "Confidential" by Abbott.

19. I read and relied upon the information contained in Abbott's various draft Descriptive Memoranda in the course of my consulting work for John Hancock. Having accurate information from Abbott concerning the condition of, and prospects for, each compound in the proposed basket of compounds was very important to me for purposes of evaluating those compounds. Although there was some data concerning each compound available from public sources, I recognized that complete, up-to-date information regarding the development status of, and Abbott's internal projections and plans for, the compounds only could come from Abbott.

20. A true and accurate copy of Abbott's initial draft Descriptive Memorandum for ABT-518 (a/k/a Abbott's "Matrix Metalloproteinase Inhibitors Program"), dated May 2000, is attached hereto as Ex. 1. I believe that Ex. 1 is one of the draft Descriptive Memoranda that I reviewed in the course of my consulting work for John Hancock in June-July 2000. That Descriptive Memorandum describes ABT-518 as a Matrix Metalloproteinase Inhibitor ("MMPI"), a family of compounds intended to inhibit the growth of cancerous tumors. It further states, in part, that:

> (a) "Abbott's Matrix Metalloproteinase Inhibitor (MMPI) program represents a novel therapeutic class, with the potential to alter the way cancer is treated by preventing or modifying disease progression and/or metastases";

(b) "The MMPI selectivity profile exhibited by ABT-518 distinguishes it from competitor's compounds"; and

(c) "ABT-518 is therefore a compelling development candidate with the potential to demonstrate antitumor effects superior to the [other] MMPI inhibitors currently undergoing clinical trials."

21. Abbott's initial Descriptive Memorandum for ABT-518 identifies other "MMPIs in Clinical Development for Cancer" as including "Marimistat" [*sic*], which reportedly was being developed by British Biotechnology and Schering Plough, and "Prinomastat," which reportedly was being developed by a combination of Agouron Pharmaceuticals, Warner Lambert and Pfizer. With respect to these competing MMPI compounds, Abbott's Descriptive Memorandum further states that,

> [a]lthough Abbott's timing to market is not optimal, the shortcomings of the competitive products provide an opportunity for a compound with an improved SE or efficacy profile. Current animal models seem to predict Abbott's compound [*i.e.*, ABT-518] is superior to those currently in clinical trials, and has the potential to be best in class.

22. A true and accurate copy of Abbott's initial draft Descriptive Memorandum for ABT-594, dated April 2000, is attached hereto as PLs' CC. I believe that PLs' CC is one of the draft Descriptive Memoranda that I reviewed in the course of my consulting work for John Hancock in June-July 2000. That Descriptive Memorandum describes ABT-594 as a new type of analgesic intended to treat moderate to severe pain, including neuropathic pain (*i.e.*, chronic pain resulting from injury to the nervous system). It further states, in part, that:

(a) "ABT-594 is a non-opioid ... analgesic that is a potent and selective cholinergic channel modulator [a/k/a neuronal nicotinic receptor agonist or NNR agonist]. It is expected to have no tolerance, dependence or abuse potential and no [U.S Drug Enforcement Agency] scheduling";

(b) Abbott's "initial targeted indication [for ABT-594] is symptomatic treatment of diabetic neuropathic pain";

(c) "The preclinical side effect and dependence liability profile of ABT-594 is superior to that of morphine";

(d) ABT-594 "has a novel mechanism of action, a potentially broad coverage of chronic pain conditions" in addition to "opioid-like efficacy without tolerance, dependence or abuse potential, while having equivalent/superior efficacy to other drugs used to treat neuropathic pain";

(e) ABT-594 was "generally well tolerated" in Abbott's prior Phase II studies of the compound, with some adverse events "includ[ing] dizziness, nausea, vomiting, asthenia, and diarrhea, all of which were considered mild by investigators"; and

(f) A further "[p]hase IIb study for neuropathic pain will begin in April, 2000 and ends [*sic*] in November, 2000" with "320 patients ... included in the study."

23. Abbott's initial Descriptive Memorandum for ABT-594 further states that ABT-594 was "expected" by Abbott "to be the first cholinergic channel modulator to receive an indication for pain," and that Abbott "expected" to make a New Drug Application (NDA) filing with the FDA for ABT-594 sometime "in 3Q2003."

24. A true and accurate copy of Abbott's initial draft Descriptive Memorandum for ABT-773, dated May 2000, is attached hereto as PLs' HX. I believe that PLs' HX is one of the draft Descriptive Memoranda that I reviewed in the course of my consulting work for John Hancock in June-July 2000. That Descriptive Memorandum describes ABT-773 as a "promising new class of antibiotics known as ketolides" that "is likely to have activity against resistant strains of bacteria and will, therefore, compete effectively against currently marketed antibiotics." It further states, in part, that:

(a) "Product features such as high efficacy, activity against resistant strains of bacteria and convenience should enable [ABT-773] to compete against both Zithromax and newer agents such as quinolones";

(b) "Dosing [of ABT-773] is expected to be once-a-day," with a "5-day convenience pack at a competitive price [that] will help maximize sales"; and

(c) "The likely profile of ABT-773" included "convenience, safety, and tolerability profile competitive with [Zithromax]" and "[o]ral suspension and I.V. forms [of ABT-773] enabling penetration into pediatrics and hospital segments."

25. Zithromax is a competing macrolide-based antibiotic that already was commercially available at the time that I conducted my analysis of ABT-773.

26. Quinolones are yet another type of antibiotic with which ABT-773 potentially would compete.

My Review and Evaluation of the Proposed Deal Compounds

27. After reviewing Abbott's draft Descriptive Memoranda and conducting some basic literature searches, I drafted and forwarded to Mr. Blewitt on June 20, 2000 a "Preliminary Analysis of Abbott Drug Basket" in which I provided him with my initial thoughts on the compounds and set out a series of issues, questions and evaluation tasks that I proposed to pursue. A true and accurate copy of that document and my cover e-mail to Mr. Blewitt is attached hereto as PLs' KU. Among the issues that I proposed to pursue was Abbott's reference to "side effects such as headaches, nausea, etc." that reportedly had been observed in some clinical trials of ABT-594, whether ABT-773 had progressed into Phase III clinical trials, and the timing of Abbott's Phase I trial of ABT-518.

28. I spent the next several weeks conducting more extensive searches of the relevant medical and scientific literature, reviewing abstracts and copies of available articles concerning the various types of pharmaceutical compounds contained in Abbott's proposed basket of compounds, and identifying and interviewing independent researchers and practicing physicians who I had reason to believe could provide useful insights regarding the technical viability and clinical attractiveness of the various compounds.

29. As my work progressed, I periodically sent summaries of my preliminary findings to Mr. Blewitt. I also began assembling a written list of unanswered questions that I intended eventually to ask of Abbott. A true and accurate copy of an example of a summary and written questions drafted about ABT-773 sent to Mr. Blewitt, dated July 4, 2000, is attached hereto as PLs' HY.

30. After I had completed my literature searches and independent interviews in mid-July 2000, I was permitted to conduct a telephone interview of an Abbott representative, Dr. John Leonard, on or about July 28, 2000, during which Dr. Leonard responded to my accumulated list of questions concerning the various proposed compounds. Abbott employees Phillip Deemer and Steven Cohen also participated in that telephone interview, as did Mr. Blewitt. I took notes of Dr. Leonard's responses to each question during the telephone conference and prepared a written summary of his responses shortly thereafter. A true and accurate copy of that interview summary with my cover e-mail message to Mr. Blewitt, dated July 28, 2000, is attached hereto as PLs' KY.

31. During the course of the interview, I specifically questioned Dr. Leonard about, among other things, the potentially small therapeutic window (*i.e.*, the ratio between the minimum dosage necessary to treat the indicated disease effectively and the maximum safe or

tolerable dosage) of ABT-594, and asked him whether Abbott regarded it as acceptable. As I recall and as reflected in my notes, Dr. Leonard responded in part by assuring me that, when Abbott gave patients the "upper-limit dose" of ABT-594, "the side-effects aren't dangerous: headache, vomiting," and that these "minor side effects" appeared "to go away over time."

32. Based on my independent review of the publicly-available literature, my discussions with various researchers and physicians, and my telephone interview with Dr. Leonard, I ultimately concluded in late July 2000 that, as best I could tell, there was "no indication of any deception on Abbott's part" with respect to the information provided in Abbott's draft Descriptive Memoranda, and that I did not see any reason for John Hancock not to move forward with its proposed investment in those compounds. My e-mail message to Mr. Blewitt containing my recommendation in that regard is included in PLs' KY.

33. Subsequent to my work in June-July 2000, I remained available to consult with John Hancock regarding any apparent change in the condition of, or prospects for, the proposed deal compounds. At no time, however, was I told or did I learn anything new about the proposed deal compounds that caused me to change my original "no deception" opinion to Hancock.

Additional Information That I Since Have Learned
About Abbott's Compounds

34. Since the commencement of this action in 2005, I have learned additional information about the pre-existing condition and prospects of some of the pharmaceutical compounds encompassed by John Hancock's Research Funding Agreement with Abbott (the "Agreement") that, I believe, would have had a material adverse effect on my recommendation to Hancock if the information had been made known to me before that agreement was signed.

35. For example, I since have learned with respect to ABT-518 that:

(a) Contrary to the representations made by Abbott in its Descriptive Memorandum for ABT-518, Abbott knew before the Agreement was signed that other pharmaceutical companies had dramatically curtailed or discontinued their own MMPI programs. Members of Abbott's management were aware no later than February 2001 that Agouron Pharmaceuticals and Pfizer had announced the prior summer that they were "stopping Phase III trials of Prinomastat in advanced prostate [cancer] and NSCLC [non-small cell lung cancer] because 'primary efficacy objectives were not met,'" and that "Marimastat development was discontinued" by British Biotech on February 15, 2001;

(b) Less than one week prior to the execution of the Agreement, the senior management of Abbott's Pharmaceuticals Division -- including Dr. Leonard -- reviewed ABT-518's current status and prospects as part of the comprehensive Initial Portfolio Prioritization Review that they conducted on March 7-9, 2001 and ordered an immediate halt to all expenditures on the development of ABT-518 due to concerns about the low prospects of success for that compound;

(c) Abbott personnel working on ABT-518 were instructed on Sunday, March 11, 2001 (*i.e.*, two days before the Agreement was executed), to "stop all development activities immediately";

(d) As a consequence of Abbott's order to stop all development activities on ABT-518 immediately because of the low prospects of success for that compound, further enrollment in the Phase I trial of ABT-518 actually was halted on or about March 12, 2001 (*i.e.*, the day before the Agreement was executed);

(e) When Mr. Deemer learned, just before the Agreement was signed, that Abbott's senior management had decided to halt further development of ABT-518, he contacted Dr. Leonard to remind him that ABT-518 was one of the Program Compounds in the planned John Hancock portfolio of compounds. Dr. Leonard, in turn, promptly spoke with other senior members of Abbott's management and reminded them of the impending Agreement with John Hancock, and suggested that Abbott proceed with the development of ABT-518; and

(f) On March 13, 2001 (*i.e.*, the day the Agreement was executed), Abbott recommenced the Phase I trial of ABT-518.

36. I since have learned with respect to ABT-594 that:

(a) Contrary to what was contained in the draft Descriptive Memorandum and what I was told by Dr. Leonard in our telephone interview, Abbott knew almost immediately after its Phase IIb trial of ABT-594 for the treatment of diabetic neuropathic pain commenced in April 2000 that Abbott encountered problems with "premature terminations" (*i.e.*, subjects dropping out of the trial early) due primarily to "adverse events" ("AEs") or side effects among trial subjects at a variety of dosing levels, including moderate-to-severe nausea, headaches, vomiting, and dizziness;

(b) By early July 2000, of the 78 subjects who had entered Abbott's Phase IIb study of ABT-594, "at least" 31 had prematurely terminated their involvement in the study due to adverse events;

(c) By August 2000, there was "much concern with the drop out rate" in the Phase IIb trial among members of Abbott's ABT-594 Product Development Team;

(d) By the Fall of 2000, members of Abbott's senior management regarded ABT-594 as having "questionable commercial viability";

(e) By mid-to-late 2000, Abbott employees with responsibility for supervising the Phase IIb trial of ABT-594 reviewed the preliminary, blinded trial data and concluded that the episodes of nausea and vomiting observed in the trial probably were dose-related. They considered, but ultimately rejected, revising the trial while it was underway to eliminate the highest dosage (*i.e.*, 300 microgram) cohort in an effort to reduce the observed rate of nausea and vomiting;

(f) By early December 2000, Abbott had decided to prematurely terminate its Phase IIb trial of ABT-594 with less than its original target of 320 patients;

(g) By December 2000, Abbott was actively seeking a co-partner to further develop ABT-594;

(h) By late 2000 or early 2001, Abbott has reduced its own planned spending on ABT-594 in Calendar Year 2001 from $35.0 million to approximately $9.3 million, a reduction of more than 73 percent;

(i) By late 2000 or early 2001, Abbott had decided to delay its previously planned additional Phase II or Phase III trials of ABT-594;

(j) By early 2001, Abbott personnel were engaged in developing a "comprehensive strategy to address tolerability issues related to NNRs for pain, including ABT-594 and follow-ons";

(k) By February or early March 2001, Abbott scientific personnel who were charged with discovering and developing new NNR compounds had concluded that "ABT-594 ... is an imperfect drug" due, in large part, to the "key adverse events of emesis, nausea, and dizziness that have consistently been observed during clinical evaluation of ABT-594"; and

(l) By early March 2001, members of Abbott's senior management had discussed what they thought would be the likely outcome of the Phase IIb trial of ABT-594 and concluded that Abbott likely would terminate further development of ABT-594.

37. I since have learned with respect to ABT-773 that:

(a) Contrary to the representations in Abbott's draft Descriptive Memorandum regarding the safety of ABT-773, Abbott had significant, unresolved issues about the safety of that compound as of March 2001, particularly with respect to the potential for abnormal heartbeat prolongation (also known as "QT" or "QTc" prolongation) and chemical-driven liver damage (also known as "hepatoxicity," "hepatotoxicity," "liver toxicity" or simply "liver tox") among clinical trial subjects who took the compound;

(b) By February 2001, Abbott internally was describing "QTc Issues" and "Liver Toxicity Issues" as "Key Issues Facing the ABT-773 development program."

Both of these "Key Issues" remained unresolved when Abbott and John Hancock entered into the Agreement just one month later; and

(c) Contrary to the representations in Abbott's draft Descriptive Memorandum that the "expected" dosing of ABT-773 was "once-a-day," Abbott recognized by June 2000 that "[u]ncertainty in ABT-773 convenience profile *i.e.* potential for [twice-a-day] dosing" as one of the "Key Commercial Issues" facing ABT-773, and concluded at least one month before the Agreement with Hancock was signed that 300 mg, once-a-day dosing of ABT-773 "was not viable" for any indication "due to high levels of diarrhea (10-20%) and taste perversion (10-20%)."

38. I believe each of the foregoing additional facts regarding ABT-518, ABT-594 or ABT-773 to be material to the condition and prospects of those compounds. I regard them as indicative of significant actual or potential problems or concerns with respect to the compounds that would cause a reasonable person or investor to seriously question or doubt the safety, efficacy, scientific viability, or commercial viability of those compounds.

39. If any of the foregoing facts regarding ABT-518, ABT-594 or ABT-773 had been disclosed by Abbott to John Hancock and to me while I still was engaged in my consulting work for John Hancock in mid-2000, I believe that those facts would have caused me, at a minimum, to inquire more deeply into the problems and concerns that they exposed or, more likely than not, to recommend that Hancock dramatically discount the perceived chances of success for those compounds or forego any investment in those compounds entirely.

40. If any of the foregoing facts regarding ABT-518, ABT-594 or ABT-773 had been disclosed by Abbott to John Hancock and to me after I largely completed my consulting

work for John Hancock in mid-2000, but before the Agreement was signed, I believe that they would have caused me, at a minimum, to recommend to Hancock that it delay the transaction and inquire more deeply into the problems and concerns that they exposed or, more likely than not, to recommend that Hancock dramatically discount the perceived chances of success for those compounds or forego any investment in those compounds entirely.

Signed under the pains and penalties of perjury this 23rd day of January, 2008.

/s/ Lynn C. Klotz
Lynn C. Klotz

CERTIFICATE OF SERVICE

I hereby certify that this document is being filed with the Court through the ECF system and that a copy will be sent electronically to counsel for defendant through the ECF system on January 28, 2008.

/s/ Richard C. Abati
Richard C. Abati (BBO No. 651037)

EX. 1

CONFIDENTIAL

Matrix Metalloproteinase Inhibitors Program

Descriptive Memorandum

May 2000

Abbott Laboratories

MMPI

Overview

Abbott's Matrix Metalloproteinase Inhibitor (MMPI) program represents a novel therapeutic class, with the potential to alter the way that cancer is treated by preventing or modifying disease progression and/or metastases. This more "chronic" approach to therapy has the potential to transform cancer into a disease that patients live with, much like the effect of HIV protease inhibitors on patients with AIDS. It also has the potential to expand the cancer market significantly by increasing the average length of treatment and expanding the pool of patients eligible to receive therapy.

The MMPs comprise a family of enzymes that degrade a wide range of matrix protein substrates. High expression of these enzymes occurs in cancer and is associated with the ability of tumors to grow, invade, develop new blood vessels and metastasize.

MMP inhibitors (MMPIs) may suppress the progression of tumors by several mechanisms:

- Suppress invasion/metastasis by blocking the membrane traversal and access to blood/lymphatic vessels
- Blocking the remodeling of extra-cellular matrix in the vicinity of primary tumors to prevent stroma-bound growth factors from stimulating tumor growth
- Blocking angiogenesis by preventing the proliferation and migration of endothelial cells and neovascularization of tumor.

Experimental evidence suggests that gelatinase A and gelatinase B are particularly important in tumor progression, consequently the project team has targeted gelatinase selective inhibitors for the treatment of cancer. Another reason for targeting highly gelatinase selective MMP inhibitors relates to the side effect profile exhibited by broad-spectrum agents like marimastat. Chronic administration of marimastat causes a dose-limiting side-effect characterized by severe joint pain and stiffness. Since these joint effects may be mediated by inhibition of other MMPs like fibroblast collagenase, highly gelatinase selective agents may be efficacious without producing dose-limiting side effects.

The MMP selectivity profile exhibited by ABT-518 distinguishes it from competitor's compounds. ABT-518 possesses sub-nanomolar inhibition potencies versus both gelatinase A and gelatinase B and is substantially more selective for the inhibition of the gelatinases over fibroblast collagenase than marimastat and prinomastat. Despite its high selectivity, ABT-518 demonstrates antitumor activity equal or superior to prinomastat. Inhibition of tumor growth is dose dependent in both syngeneic and xenograft models. ABT-518 is also effective in blocking vessel formation in a mouse model of angiogenesis. ABT-518 is a stable crystalline solid which can be synthesized in six steps (25% overall yield) from commercial starting material.

ABT-518 gives rise to sustained plasma concentrations following single oral dosing in monkeys, dogs and rats. Bioavailabilities range between 68 and 93% depending on formulation and species. Several metabolites are produced after repeated oral dosing of ABT-518, although their relative amounts varies with gender and species.

ABT-518 displays no meaningful effects in genotoxicity, cytotoxicity and ligand binding assays and its cardiovascular effects in dogs are unremarkable. ABT-518 produces no significant toxic effects in rats treated with 100 mg/kg/day over 28 days. Plasma concentrations generated by ABT-518 in these studies are at least 20-fold higher than those necessary to produce efficacy in cancer animal models. ABT-518 is therefore a compelling development candidate with the

potential to demonstrate antitumor effects superior to the MMP inhibitors currently undergoing clinical trials.

The market

Currently, cytotoxic agents represent the largest, and fastest growing, class of oncology agents by sales volume. The following chart summarizes the value of the current oncology market.

Global Sales by Market Segment ($ MM)

	1996 Sales	1997 Sales	1998 Sales	1999 Sales (est)	CAGR '96-'98
Hormone	4,414	4,784	4,884	5,000	5.2%
Cytotoxic	4,278	5,212	6,258	7,300	21.0%
Adjunctive	3,367	3,651	4,166	4,900	11.2%
Total	12,059	13,647	15,318	17,200	12.7%

Source: Datamonitor

Sales by Region ($ MM)

	1996 Sales	1997 Sales	1998 Sales	1999 Sales (est)	CAGR '96-'98
US	5,564	6,276	7,422	8,500	15.5%
Ex-US	6,495	7,370	7,895	8,700	10.3%

Source: Datamonitor

Cytostatic agents have the potential to alter the way cancer is treated and presents opportunities for fundamentally new ways of approaching the disease. This cytostatic market does not yet exist, though success of more cytostatic "like" treatments, such as hormonal therapies for prostate and breast cancer, suggest that the market potential for cytostatic agents could be significant.

The ultimate commercial and clinical success of the MMPI will depend on the clinical benefit this product provides in key cancer types compared with current best therapy. These can be benefits provided by dosing this agent in addition to current therapy and/or as an alternative to best therapy, or as a new component of best therapy. All currently available products, including the market leaders such as Taxol, have significant shortcomings in their profiles.

However, as novel therapy, MMPIs will probably be adopted initially as add-on the current chemotherapy. As benefits are proven and clinical experience is gained, these agents may be used in earlier stages of cancer and/or in conjunction with surgery or radiation to prevent the progression of any microscopic disease that remains.

The clinical targets identified for this compound include late stage pancreatic cancer, late stage NSCL cancer (on-label), with late stage ovarian and breast cancer as additional cancer types where efficacy has been demonstrated, but not filed. Other cancer types this compound may be efficacious in include SCL, colorectal, bladder, stomach and prostate. Targets will be refined as we know more about this compound's in-vivo activity.

The following tables summarize the key marketed competitive products by indication (US data only):

Late Stage Breast

Product	Share
Cyclophosphamide/Cytoxan/BMS	18.7
Doxorubicin/Adriamycin/P&U	17.11
Docetaxel/Taxotere/RPR	16.25
Paclitaxel/Taxol/BMS	16.11
Trastuzumab/Herceptin/Genetech	11.26

Late Stage NSCL

Product	Share
Carboplatin/Paraplatin/BMS	50.32
Paclitaxel/Taxol/BMS	44.14
Vinorelbine/Navelbine/Glaxo	22.78
Gemcitabine/Gemzar/Lilly	22.14
Cisplatin/Platinol/BMS	11.28

Late Stage Ovarian

Product	Share
Paclitaxel/Taxol/BMS	47.11
Carboplatin/Paraplatin/BMS	45.42
Topotecan/Hycamtin/SKB	22.54
Dox SL/Doxil/Alza	9.14
Cisplatin/Platinol/BMS	7.58

Late Stage Pancreas

Product	Share
Gemcitabine/Gemzar/Lilly	78.5
5-FU/Efudex/ICN Pharma	21.0
Leucovorin/	10.7
Cisplatin/Platinol/BMS	4.72

Compounds in Development

The MMP inhibitor field is competitive. More than 30 firms have filed patents claiming small molecule MMP inhibitors over the past 5 years, and several companies have compounds in advanced clinical development. Abbott's compound may be 3rd or 4th to market and will have to demonstrate a competitive advantage to gain the share necessary to support the clinical development of this compound. Companies with compounds in advanced clinical development for the treatment of cancer include Agouron/Warner Lambert/Pfizer, British Biotechnology/Schering Plough and BMS and are listed below. Other companies are targeting this mechanism for arthritis.

MMPIs in Clinical Development for Cancer

Compound	Company	Comments	Phase
Marimistat	BritishBiotechnology/ Schering Plough	Broad spectrum, dose limiting toxicity. Activity seen in gastric cancer, but negative results in pancreatic.	III
Prinomastat	Agouron/ Warner Lambert/ Pfizer	Moderate gelatinase selectivity, dose limiting toxicity. May be dosing sub-optimally to avoid toxicity. Efficacy data not available.	III
BMS 275291	BMS	Broad spectrum, joint effects seen in Phase I studies.	II

Bayer recently dropped development of BAY 12-9566 due to concerns about potential toxicity. Recent results from a study with marimistat in pancreatic cancer, where adding marimistat to Gemzar resulted in no survival advantage, has led to speculation that MMPIs may be more applicable in less aggressive cancer types or earlier stages of the disease. Alternatively, it could be a reflection of the inability to examine higher doses of marimastat due to joint effects.

The joint effects produced by the compounds listed above almost certainly preclude their long-term use, limit compliance and reduce optimal efficacy. Any MMP inhibitor that lacks these side effects will possess a substantial competitive advantage. The musculoskeletal effect produced by marimastat and prinomastat in cancer patients is typically described as arthralgia, myalgia and tendinitis, which occurs predominately in the upper limbs. While mild cases respond to analgesics, interrupting therapy for a period of approximately 2 weeks is necessary when the condition is less well tolerated.

Although Abbott's timing to market is not optimal, the shortcomings of the competitive products provide an opportunity for a compound with an improved SE or efficacy profile. Current animal models seem to predict Abbott's compound is superior to those currently in clinical trials, and has the potential to be best in class.

Product profile

The objective of a product profile at this time in the product's development is to provide a target for the types of attributes that will be required to be commercially successful. This profile is based on market research with oncologists and consultation with opinion leaders. This profile will continue to be refined as more is known about this product's profile, development of competitive products and the market continues to evolve.

	Base	Optimal
Efficacy	ABT-518, alone or in combination with best therapy, provides at least one of the following benefits in at least one solid tumor type: • Increased survival • Tumor regression • Improved quality of life • Increased time to tumor/disease progression	Provides more than one of the efficacy benefits outlined.
Competitive advantage	ABT-518 will need to demonstrate a clinically significant advantage in efficacy (see parameters above) or additive synergistic activity with current/competitive agents or clinically significant advantage in side-effect profile relative to other MMPI agents.	Same
Administration	Convenient administration relative to competitive agents.	Same plus reimbursement in US market.
COGS	A finished cost of goods that is consistent with at least an 80% standard manufacturing margin.	A finished cost of goods that is consistent with at least a 90% standard manufacturing margin.

Marketing overview

Product Usage: Physicians have indicated that they would use MMPIs initially in their more refractory patients, as follow-on or add-on to current best therapy (chemo or surgical). With experience and clinical evidence, they would be willing to use these agents in earlier stages of the disease, where they perceived the greatest benefit to be. The MMPI was regarded as a maintenance therapy to be used in early disease or after primary therapy as a prophylactic process to prevent the spread of malignancy.

Product Benefits/Efficacy: Physicians are looking for improvements in time to tumor progression and prevention of metastases with cytostatic agents. The MMPI mechanism has more recently been implicated as having an even more active role in cancer pathogenesis, from preventing primary tumor growth to anti-angiogenic properties. Positive results from competitive agents, such as marimistat in gastric cancer, provides proof of principle for this mechanism.

Side Effects: The proposed safety profile of MMPIs (excluding joint toxicity) may enhance usage, as the dose limiting toxicity profiles of most of the other available agents has established a much lower hurdle for demonstrating a preferred profile. However, as chronic therapy, MMPIs may *have* to demonstrate a cleaner profile than cytotoxic agents do to ensure compliance. As the 3rd or 4th MMPI to market, SE hurdles will be even higher for this compound. As a critical Go/No Go decision point, the joint toxicity of this compound will be evaluated in an expanded Phase I multi-dose study.

Dosing: Discovery is currently targeting an oral dosage form. In general, oral therapies are acknowledged by physicians and patients as being more convenient to the patient. Chronic oral dosing may also reduce overall costs, as infusion support products and personnel would not be required, enhancing pharmacoeconomic evidence.

COGS: Initial estimates on finished cost of drug suggest that drug costs will not be significant for this compound. With the pricing flexibility in the US market, PPD should be able to get more than 90% margin on this product.

Off-label use: Off label use accounts for between 30-60% of an oncology product's usage. Off-label use is driven by publication of clinical trial results in credible journals, listing in key compendia and/or a peer's experience with the product. Therefore, development spend for off-label use is considerably less than the spend required for regulatory approval of an indication. However, promotion of these off-label uses is limited.

Competition: As the 3rd or 4th MMPI to market, Abbott's compound will need to demonstrate a meaningful clinical advantage over compounds that are in more advanced development. Strict Go/No Go criteria will determine if the MMPI can meet these hurdles. If they cannot be met, the compound will not move forward.

Development/Regulatory: With a new class of compounds, there is not a clearly defined clinical development path or regulatory guidelines for reference. This hurdle is similar for all the competitive products, but increases the overall development risk profile for these agents. However, with several MMPIs in late stage development, Abbott can learn from their experience.

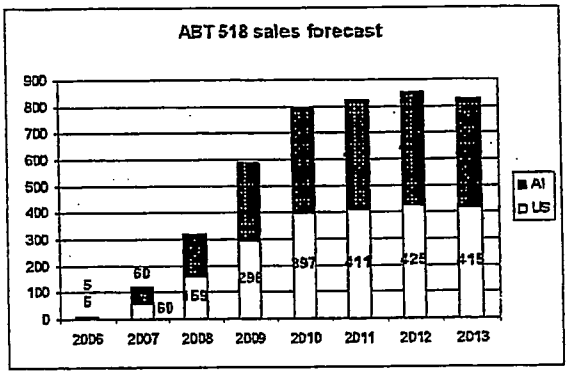
Other Approaches: Other "cytostatic" approaches may present a competitive threat if they are used as substitutes. Due to the complexity of the pathogenesis of cancer, it is more likely that these agents will be used in combinations, but incremental benefits may become more difficult to demonstrate as the number of products and approaches multiply. This will require additional studies, as these other classes become part of standard cancer treatment. However, this threat is not unique to this compound.

Pricing: The treatment of cancer is expensive, so there is the potential for a great deal of pricing flexibility in this market. However, as an oral therapy in the US market, there may be additional downward price pressure for this agent. There is also an increasing emphasis on cost-effectiveness studies that will need to be addressed in the development plan.

Dosing: Discovery is currently targeting an oral dosage form. In general, oral therapies are preferred by physicians and patients because of the convenience to the patient. However, this form may not be the best choice for some people who already have certain digestive system symptoms (vomiting, diarrhea, or severe nausea), cannot swallow liquids or pills, or cannot remember when or how many pills to take. Additionally, in the US market there are several unique factors that currently do not favor oral therapies. Novel oral therapies are not currently reimbursed by Medicare, a significant payer for the oncology patient population. Also, 40-60% of a community oncologist's income is generated through the administration of IV drugs. An oral therapy would not be a source of revenue to the physician.

Financial Projections

A product forecast was developed for the US and ex-US markets.



Clinical Studies

Clinical studies across a wide range of solid tumors will be initiated, including but not limited to breast cancer, non small cell lung cancer, ovarian cancer, pancreatic cancer, etc...

Final indications pursued will depend from the results of the phase II studies.

Patent Status

The patent is estimated to expire in August of 2018.

PLs' CC

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ABT – 594

Descriptive Memorandum

April 2000

Abbott Laboratories

ABT-594

Opportunity Overview

ABT-594 (the "Product") is a non-opioid, non-NSAID analgesic that is a potent and selective cholinergic channel modulator. It is expected to have no tolerance, dependence or abuse potential and no DEA scheduling. ABT-594 is orally-administered, and BID dosing is expected. Its initial targeted indication is symptomatic treatment of diabetic neuropathic pain.

The IND filing of ABT-594 was in 1Q1998. A Phase IIb (dose ranging) trial will begin April 2000 in neuropathic pain. A Go/No Go decision for clinical efficacy is expected February 2001. The NDA filing is expected in 2Q2003. Development of additional formulations is under consideration (parenteral, transdermal, extended-release). Total world wide peak sales of ABT-594 are projected to reach over $800MM by 2009.

The US Market of Neuropathic Pain

Pain is the most common symptom of disease and the most frequent complaint with which patients present to physicians. The economic burden of pain in the United States is estimated at $100 billion a year in direct and indirect costs. Approximately 95 MM Americans per year receive drug therapy for pain, which represents about 50% of those who suffer from pain.

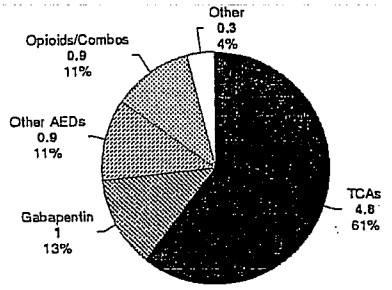
Despite its prevalence, pain is often inadequately managed. There have been few major advances in pain therapy over the last several decades, and pain management continues to rely on nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, opioids and certain adjuvant analgesics.

In the last five to ten years, advances in neurobiology and the development of more sophisticated animal models of clinical pain have led to a paradigm shift in the understanding of pain mechanisms. Not all pain states are the same, and different mechanisms may contribute to pain caused by non-injurious stimuli (acute nociceptive pain), by tissue injury (inflammatory pain) and by nerve injury (neuropathic pain). Tissue and nerve injury induce changes in pain pathways in the nervous system, resulting in altered processing of noxious and non-noxious sensory information, and reveal molecular targets which may not be involved in the processing of sensory information from healthy tissue.

Neuropathic pain is a very large, yet largely untapped market. Estimates vary widely for the number of worldwide sufferers, from as low as 20 million to as high as 50 million or more. The number of actual cases is difficult to estimate since neuropathic pain is difficult to diagnose, and is often misdiagnosed.

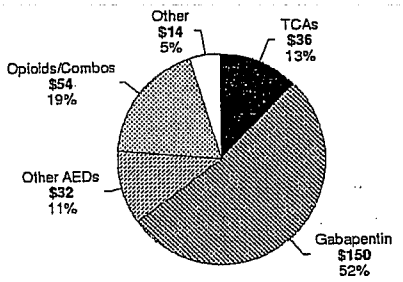
Neuropathic pain is often treated with adjuvant analgesics such as tricyclic antidepressants, anticonvulsants and alpha adrenergic agonists. In the U.S. alone, approximately $200 million of the sales of the anticonvulsant Neurontin (gabapentin) are off label uses attributed to the treatment of neuropathic pain. However, a significant unmet need exists in the treatment of neuropathic pain since few medications provide complete pain relief and most adjuvant medications have significant side effects that preclude their long-term use. As more effective and tolerable medications become available, the neuropathic pain market is expected to experience significant growth.

U.S. Neuropathic TRx (MM)



1998 Neuropathic Pain TRx = 8 MM

U.S. Neuropathic TRx Sales ($MM)



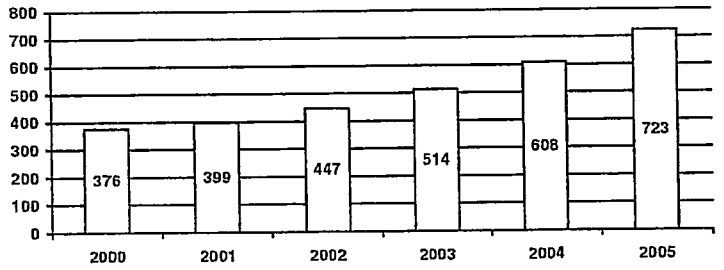
1998 Neuropathic Pain TRx Sales = $286 MM

Sources: IMS Audits and Decision Resources 9/99 Neuropathic Pain Report

US Market Projections

The US neuropathic pain market is expected to grow at a double digit, as a result of the introduction of new therapies (e.g. pregabalin in 2001) , the continued increase in physicians' awareness of anti-convulsants' utility as analgesics, and the expansion in the prevalent population. The market is projected to reach over $700MM in 2005.

US market forecast ($MM)



Sources: Abbott analysis

Scientific Rationale for ABT-594

Recent findings in the understanding of pain mechanisms have led to a new conceptual approaches to clinical pain and a new understanding of potential novel molecular targets for analgesic drug development. Molecular targets have included modulators of glutamate neurotransmission (NMDA antagonists), ion channel modulators (neuron specific calcium channels, TTX-resistant sodium channels), neurokinin antagonists (NK-1), and novel anti-epileptics targeting the calcium receptor. None of these approaches has yet produced compounds exhibiting broad-spectrum analgesic efficacy with decreased side effect liability. A significant unmet need exists in the pain management market for products that are safer, non-abusable, non-addicting, non-scheduled, non-tolerance producing, and efficacious in oral and parenteral forms for the treatment of moderate to severe pain, especially for chronic nociceptive and neuropathic pain.

ABT-594 is a non-opioid, non-NSAID analgesic that is 30- to 100-fold more potent and equally efficacious to morphine in treating moderate to severe pain in several well-characterized animal models of nociception. The preclinical side-effect and dependence liability profile of ABT-594 is superior to that of morphine. Mechanistically, ABT-594 is a potent and selective cholinergic channel modulator (ChCM) with high oral bioavailability in rat, dog, and monkey.

ABT-594 is expected to be a highly differentiated product. It is expected to be the first cholinergic channel modulator to receive an indication for pain. It has a novel mechanism of action, a potentially broad coverage of chronic pain conditions. In addition, it has an opioid-like efficacy without tolerance, dependence or abuse potential, while having a equivalent/superior efficacy to other drugs used to treat neuropathic pain.

Clinical Studies

In pre-clinical studies, ABT-594 rapidly distributes to the brain following systemic administration and, like morphine, can work at multiple levels in the central and peripheral nervous systems to modulate pain perception. ABT-594 produces antinociceptive effects by interacting at both central and peripheral nAChRs. Injections of ABT-594 into brain at doses 1000-fold lower than given peripherally produce marked antinociceptive activity, indicating that ABT-594 can also activate descending pathways from the CNS to modulate pain processing. It also inhibits the release of the primary nociceptive transmitters, substance P and calcitonin gene related peptide (CGRP) *in vitro,* at the level of the dorsal horn of the spinal cord suggesting that ABT-594 can attenuate mechanisms leading to neurogenic inflammation, central sensitization and consolidation of pain-mediated neuronal changes.

Human clinical trials began in 1997. Phase I trials with an oral solution formulation indicated that 150ug/day would be the maximally tolerated dose. In subsequent phase I and phase II trials with soft elastic capsule (SEC) and hard gelatin capsule(HGC) suggest that higher doses would be tolerated. A phase IIa study with ABT-594 SEC formulation suggests a trend towards analgesic effect at 75ug BID. ABT-594 is generally well tolerated in the dose range. Adverse events include dizziness, nausea, vomiting, asthenia, and diarrhea, all of which were considered mild by investigators.

Phase IIb study for neuropathic pain will begin in April, 2000 and ends in November, 2000. 320 patients will be included in the study.

Patent Status

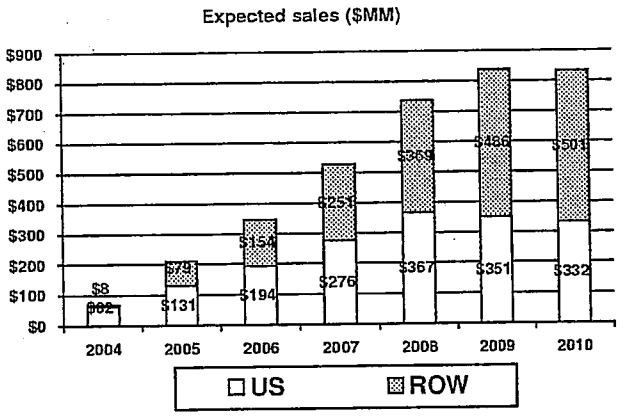
A patent has been granted from the United States Patent and Trademark Office on an application providing generic coverage for ABT-594 and a large class of structurally related analogs. The original filing date for

this application dates back to October 9, 1992. The expiration of patent coverage for composition of matter for ABT-594 will be June, 2016.

An additional application (6013.US.01), which includes species claims to ABT-594 as well as use claims for the treatment of pain, was filed in December, 1996 and is pending. If this patent is allowed, it will provide 20 years from date of filing, which will extend the patent life of ABT-594 and ABT-259 to December, 2016.

The original application providing generic composition of matter coverage was filed broadly ex. U.S. (WO94/08992) and this application published on April 28, 1994. A second foreign filing (WO96/40682) published on December 19, 1996. These cases are all still pending.

Financial Projections



Assumptions for Financial Projections

- Base Case assumes Neuropathic Pain claim and published study in Chronic Nociceptive Pain
- Filed 5/03, Launched 5/04
- MD targets 20% FP/GP/IM, 50% Neuro, 25% Rheum
- Price based on Ultram, '98 AWP $2.72/day, increases 2%/year
- Peak Share 10% for Persistent Chronic Pain, 20% for NP, both in Yr 5

Appendix 1

Key BPH Products in Development – Phase II and Higher

Product	Company	US Dev Phase	Class/MOA	Comments
pregabalin	Parke-Davis	III	Ca channel alpha2delta	Also for epilepsy, chronic pain
GV 196771	Glaxo	II	glycine antagonist	Neuropathic pain & chronic pain
memantine	Merz	II	NMDA antagonist	Dose ranging trial with 375 patients now underway
PN 401	ProNeuron	II	Unknown	For disease modification of PDN - pain & numbness next
prosaptide	Myelos	II	Unknown	14 amino acid peptide Pain associated with nerve injury
resiniferatoxin	Afferon	II	vanilloid	Topical capsaicin analog
LTA	Astra	II	sodium channel blocker	Topical w/ longer duration of action than capsaicin
CNS 5161	Cambridge Neuroscience	I	NMDA antagonist	Will not move to Ph II until a development partner is found

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ABT – 773

Descriptive Memorandum

May 2000

Abbott Laboratories

ABT-773

Opportunity Overview

ABT-773 pertains to a promising new class of antibiotics known as ketolides. ABT-773 is likely to have activity against resistant strains of bacteria and will, therefore, compete effectively against currently marketed antibiotics. The compound is currently in Phase IIb trials. It is scheduled to begin in phase III clinical trials in Q4, 2000 and has an expected U.S. launch date of January 2003. Ex-U.S. launches are projected for 2003 and 2004 for Europe and Japan, respectively.

Product features such as high efficacy, activity against resistant strains of bacteria and convenience should enable it to compete against both Zithromax and newer agents such as the quinolones. Dosing is expected to be once-a-day. A 5-day convenience pak at a competitive price will help maximize sales. Worldwide sales, including tablet/capsule, oral suspension and intravenous (I.V.) forms, are projected to top $1 billion by 2007.

The US Market

The overall antibiotic market in the U.S. reached $8.9 billion in sales in 1999. The tab/cap segment is the largest; sales in 1999 were $5.7 billion. The I.V. and oral suspension segments are comparatively smaller; total sales topped $2.1 and $1.1 billion, respectively.

Tab/cap and oral suspension prescription volume had been declining 1-2% per year in the period of 1995-1998, due to more appropriate prescribing in the face of increasing resistance. However, total tab/cap prescription volume recovered in 1999 and grew 6.3%. Even in the face of negative pressure on antibiotic use, dollar sales in the U.S. have continued to increase, particularly in the tab/cap market. This is due to the trend of replacing relatively low-cost generic agents with higher priced premium antibiotics. The market is willing to bear higher costs for agents that satisfy unmet needs. The I.V. market has grown slightly in terms of sales, also being driven largely by the replacement of generic agents with more costly branded agents.

Macrolides, largely fueled by the gains of Zithromax, have seen significant growth in terms of both prescriptions and sales. Zithromax prescriptions far outnumber those of other competitors, while its sales have nearly surpassed those of the sales leader, Cipro. Historically, quinolones saw relatively limited use for community respiratory tract infections (RTIs) because of poor Gram-positive coverage and sub-optimal adverse event profiles. Newer quinolones such as Levaquin have been successful in achieving more widespread use by virtue of its improved activity and adverse event profile. Levaquin currently accounts for approximately 30% of quinolone market share. It is anticipated that recent quinolone introductions (Avelox, Tequin) will build upon the RTI momentum established by Levaquin. The growth of the macrolide and quinolone classes has come largely at the expense of cephalosporins and generic agents such as erythromycin and penicillin.

The following table shows 1999 tab/cap sales and prescriptions by class/product:

	Sales			TRXs		
	Sales ($MM)	Share	$CAGR_{95\text{-}99}$	TRXs (MM)	Share	$CAGR_{95\text{-}99}$
Penicillins	$148.3	2.6%	-1.0%	52.5	23.7%	-5.6%
Cephalosporins	$980.9	17.2%	-5.8%	37.9	17.1%	-3.5%
Ceftin	$383.9	6.7%	1.8%	5.0	2.3%	-1.0%
Cefzil	$188.7	3.3%	12.5%	2.7	1.2%	11.3%
Other	$408.3	7.1%	-14.7%	30.1	13.6%	-4.8%
Ext. Spec. Macrolides	$1,595.6	27.9%	19.9%	36.1	16.3%	20.8%
Biaxin	$690.5	12.1%	6.1%	11.3	5.1%	1.2%
Zithromax	$891.1	15.6%	42.1%	24.4	11.0%	41.5%
Other	$14.0	0.2%	21.0%	0.4	0.2%	53.0%
Quinolones	$1,622.1	28.4%	17.0%	24.0	10.8%	11.7%
Cipro	$902.5	15.8%	8.3%	14.1	6.4%	5.1%
Levaquin	$529.4	9.3%	NA	7.0	3.1%	NA
Other	$190.2	3.3%	-2.2%	3.0	1.3%	-6.4%
Augmentin	$778.1	13.6%	17.8%	10.7	4.8%	11.8%
Other Classes	$590.5	10.3%	-1.1%	60.4	27.3%	-4.1%
TOTAL TAB/CAP	$5,715.4	100.0%	8.9%	221.5	100.0%	0.1%

U.S. Market Projections

Resistance to antibiotics is likely to increase, creating opportunities for new agents with activity against resistance. Physicians will be urged to choose agents with an appropriate spectrum of activity relative to the infection being treated. Resistance will increasingly become part of the promotional mix for emerging agents. The ability of an agent to treat resistant strains and the real or perceived ability to slow or prevent resistance development (mutation prevention concentration, low mutation frequency, structure-activity relationships, etc) may confer competitive advantage to such agents.

- Quinolones, which historically have seen limited use in community-acquired respiratory infections, will become a significant class in this segment as new agents from this class are launched that specifically target RTIs.

- The market will become more competitive as new agents enter both the community segment (ketolides, quinolones) as well as the nosocomial segment (oxazolidinones, streptogramins, everninomycins, peptides, others).

- Several key branded antibiotics will lose patent exclusivity over the next three to five years.. This may create an opportunity in the pediatric market as the top three pediatric brands (Augmentin, Cefzil, Zithromax) are among those losing patent exclusivity.

Antiviral influenza and cold therapeutics, as well as an increasing number of antibacterial vaccines may have a negative impact on antibiotic prescriptions.

The Ex-U.S. Market

Ex-U.S. sales of antibiotics totaled $11.7 billion in 1999. Tab/cap represents the largest segment, with sales of $9.4 billion from 770 million total prescriptions. Total Rx growth has been flat, with a 1996-99 CAGR of 0.5%. The use of antibiotics is predicted to slowly decline due to more judicious use of antibacterials in the face of increasing bacterial resistance.

Ex-U.S., the quinolone class accounted for 8% of total tab/cap market prescriptions (62 million Rxs) and 13% of sales ($1.2 billion). Ciprofloxacin is the market leader ex-U.S. with approximately 47% of the quinolone market Rxs (29 million Rxs) and 44% ($530MM) of sales. Levofloxacin launched in many European markets in 1998/1999 and holds approximately 14% Rx share of the European quinolone market and 0.8% of the overall tab/cap market. Although grepafloxacin and trovafloxacin also launched in some European countries in 1999, both products were recently pulled from the market due to liver toxicity and other complications. Moxifloxacin launched in Germany in Q4 1999, but has not yet been approved in other markets. In Japan, levofloxacin launched in 1994 and still commands a 65% Rx share of the quinolone market and 10% of the Japanese tab/cap market overall. Japan accounts for approximately 80% of ex-U.S. levofloxacin sales ($370MM).

Scientific Rationale for ABT-773

The likely profile of ABT-773 justifies further development:

- ABT-773 pertains to a new class of antibiotics.
- Good activity against resistant gram + organisms, particularly macrolide resistant S. pneumoniae.
- Convenience, safety, and tolerability profile competitive with Z-pak.
- Oral Suspension and I.V. forms enabling penetration into pediatrics and hospital segments.

Clinical Studies

The safety and efficacy of ABT-773 in AECB were studied in a multi-center Phase II clinical trial conducted between January and April of 1999. Dosing regimens of 100mg TID and 200mg TID were tested. Of the 169 enrolled patients, 159 were clinically evaluable and 96 were both clinically and bacteriologically evaluable. The following chart summarizes the results.

Presumed Bacterial Eradication	ABT-773 100mg TID	ABT-773 200mg TID	Overall Eradication
S. pneumoniae	100% (13/13)	90% (9/10)	96% (22/23)
M. catarrhalis	100% (6/6)	100% (7/7)	100% (13/13)
H. influenzae	96% (23/24)	92% (24/26)	92% (47/50)
H. parainfluenzae	100% (6/6)	88% (7/8)	93% (13/14)

Clinical Response	ABT-773 100mg TID	ABT-773 200mg TID
Cure	96% (77/80)	92% (73/79)
Failure	4% (3/80)	6% (3/48)

Clinical and Bacteriological Response	ABT-773 100mg TID	ABT-773 200mg TID
Cure	96% (46/48)	94% (45/48)
Failure	4% (2/48)	6% (3/48)

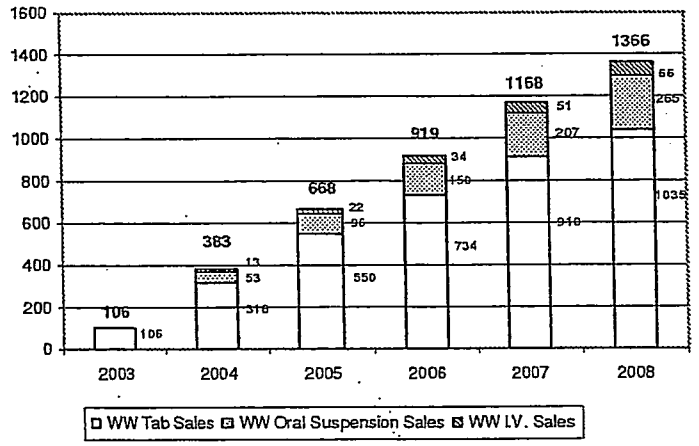
Adverse Events	ABT-773 100mg TID	ABT-773 200mg TID	Overall
Taste Perversion	5% (4/84)	8% (7/85)	6.5% (11/169)
Diarrhea	11% (9/84)	6% (5/85)	8% (14/169)
Nausea	2% (2/84)	2% (2/85)	2% (4/169)
Abdominal Pain	1% (1/84)	2% (2/85)	2% (3/169)
Headache	2% (2/84)	1% (1/85)	2% (3/169)
Rash	2% (2/84)	1% (1/85)	2% (3/169)
Dyspnea	2% (2/84)		1% (2/169)
Elev. Liver Funct. Test	1% (1/84)	1% (1/85)	1% (2/169)
Fever		2% (2/85)	1% (2/169)

Patent Status

ABT-773 will have patent exclusivity through 2016.

Financial Projections

Total Worldwide ABT-773 Net Sales ($MM)



Total Worldwide ABT-773 Net Sales by Form ($MM)

	2003	2004	2005	2006	2007	2008
US Tablet Sales	64	159	289	383	481	570
US Oral Suspension Sales		41	59	88	123	162
US I.V. Sales		12	18	26	37	48
Total U.S. Sales	64	212	366	497	641	780
Ex-US Tablet Sales	43	157	261	352	430	465
Ex-US Oral Suspension Sales		12	38	63	84	103
Ex-US I.V. Sales		1	4	8	14	18
Total Ex-US Sales	43	170	303	423	528	586
Total Worlwide ABT-773 Sales	106	383	668	919	1168	1366

Assumptions for Financial Projections

- The tab form of ABT-773 launches in the U.S. and ex-U.S. in 2003; I.V. and oral suspension launch in 2004.
- 5 day QD compliance pak available.
- ABT-773 priced competitively with other macrolides, ketolides and quinolones in market at time of launch.
- Efficacy against multi-drug resistant Strep. pneumoniae is main point of differentiation vs. beta-lactam, macrolide and quinolone antibiotics.
- Tolerability equivalent to Zithromax.

- **Appendix 1**

Key Emerging Competitors

Generic	Brand	Company	Class	Status
moxifloxacin	Avelox	Bayer	Quinolone	Approved by FDA 12/13/00
gatifloxacin	Tequin	BMS	Quinolone	Approved by FDA 12/21/00
gemifloxacin	Factive	SKB	Quinolone	Filed NDA 12/15
T-3811	TBD	BMS/Toyama	Quinolone	Phase I
telithromycin	Ketek	Aventis	Ketolide	Filed NDA 3/00
linezolid	Zyvox	Pharmacia	Oxazolidinone	Approved by FDA Q2 '00

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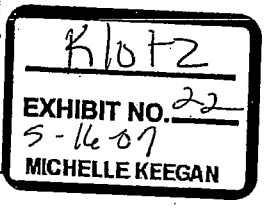


From: Lynn C. Klotz [LynnKlotz@compuserve.com]
Sent: Tuesday, July 04, 2000 12:30 PM
To: Blewitt, Stephen
Subject: ketolide research summary

Steve,

Here is the summary research on ketolide antibiotics. This might be the most promising of Abbott's single drugs in the package. It may even achieve the greater than $1 billion market share they project, since Adventis publically projects $1 billion for its ketolide, Ketek, just on the market. Abbott's is not far behind and may have superior properties.

I will complete the summary research writeups on the trip, and send them to you when I return shortly after July 10.

As far as a final report, I will make sure you have all the information verbally first. I am planning one page for each basket item which will summarize the most salient facts. The interviews and slightly polished research summaries will be in Appendices.

-Lynn

Abbott's Ketolide Antibiotic (ABT-773)

file: abbott-ketolide

Potential interviewee's for ABT-773

Stuart Levy (Professor Microbiology Tuft's University School of Medicine, Tel: 617-636-6764, e-mail: stuart.levy@tufts.edu) is a leading authority on antibiotic resistance. If he views ketolides as particularly promising we may not need to interview anyone else.

Malathum K, Coque TM, Singh KV, Murray BE
(*Good interview candidates*)
Center for the Study of Emerging and Re-Emerging Pathogens, University of Texas Medical School, Houston 77030, USA.

Schulin T, Wennersten CB, Moellering RC Jr, Eliopoulos GM
Department of Medicine, Beth Israel Deaconess Medical Center, and Harvard Medical School, Boston, MA 02115, USA.
(Excellent interview candidates, because of local connection. Does Andy Onderdonk know these researchers)

Strigl S, Roblin PM, Reznik T, Hammerschlag MR
Division of Infectious Diseases, Department of Pediatrics, State University of New York Health Science Center at Brooklyn, Brooklyn, New York 11203-2098, USA.
(*Possible interview candidates*)

Questions for antibiotic resistance experts on ketolide antibiotics

What new classes of antibiotics show promise against resistant gram-positives?

Of the following new classes, which are the most promising: Quinolones, polyketides, macrolides, ketolides, others? Why?

On average, what percentage of gram-positive infections are resistant to antibiotics? How fast is resistance growing?

Which of the large drug companies do you see as leaders in the development of new antibiotics?

The antibiotic market is highly fragmented. In business terms, there are many antibiotics each with small market share. What would be the properties of a new antibiotic that would make it widely used? Of the development stage antibiotics, do you see one or more that should find wide usage, and thus large market share?

Are there any other approaches to protection against infections that will significantly compete

with antibiotics? Vaccines? Vaccines in edible plants? Others?

Are there any other approaches to antribiotic resistance, besides new antibiotics, that seem promising?

Is there a key question that I did not ask? What is it, and how would you answer it?

Questions for Abbott on ABT-773 and competition

HMR 3647 is a Hoechst Marion Roussel antibiotic. It appears in more than one recent paper as especially promising. In view of the fact that Aventis is the name of the Hoechst/Rhone-Poulenc merger, is Ketek just the new name for HMR 3647?

Is ABT-773 also more effective against strains susceptible to other antibiotics?

What other new classes of antibiotics show promise against resistant gram-positives?

On average, what percentage of gram-positive infections are resistant to antibiotics? How fast is resistance growing?

In one literature report of a comparative test between Hocest's ketolide (HMR 3647) and ABT-773, ABT-773 was found to be more active. Are there other ketolides for which you have comparisons?

How did you arrive at future sales of over $1.3 billion?

Example articles

2: Antimicrob Agents Chemother 2000 Jun;44(6):1562-7
Studies of the novel ketolide ABT-773: transport, binding to ribosomes, and inhibition of protein synthesis in streptococcus pneumoniae.
Capobianco JO, Cao Z, Shortridge VD, Ma Z, Flamm RK, Zhong P
Infectious Disease Research, Abbott Laboratories, Abbott Park, Illinois 60064, USA.
[Medline record in process]
Macrolide resistance in Streptococcus pneumoniae has been associated with two main mechanisms: target modification by Erm methyltransferases and efflux by macrolide pumps. The ketolide ABT-773, which has a 3-keto group and no L-cladinose sugar, represents a new class of drugs with in vitro activity against a variety of resistant bacteria. Several approaches were undertaken to understand how ABT-773 was able to defeat resistance mechanisms. We demonstrated tighter ribosome binding of ABT-773 than erythromycin. We also showed that ABT-773 (i) accumulated in macrolide-sensitive S. pneumoniae at a higher rate than erythromycin, (ii) was able to bind with methylated ribosomes, though at lower affinities than with wild-type ribosomes, and (iii) accumulated in S. pneumoniae strains with the

efflux-resistant phenotype. (*Abbott has done research on the resistance mechanism.*)
PMID: 10817709, UI: 20277881

3: Antimicrob Agents Chemother 2000 Apr;44(4):1112-3
In vitro activity of ABT 773, a new ketolide antibiotic, against Chlamydia pneumoniae.
Strigl S, Roblin PM, Reznik T, Hammerschlag MR
Division of Infectious Diseases, Department of Pediatrics, State University of New York Health Science Center at Brooklyn, Brooklyn, New York 11203-2098, USA.
(*Possible interview candidates*)
The in vitro activities of ABT 773, telithromycin (HMR 3647), azithromycin, clarithromycin, erythromycin, and levofloxacin were tested against 20 strains of Chlamydia pneumoniae. (*Good, this is a comparative test between Hocest's ketolide and Abbotts*) The MIC at which 90% of the isolates were inhibited and the minimal bactericidal concentration at which 90% of the isolates were killed by ABT 773 were 0.015 microg/ml (range, 0.008 to 0.015 microg/ml). ABT 773 was the most active antibiotic tested in this study. (*This is in vitro, what about comparative animal studies?*)
PMID: 10722526, UI: 20187185

4: Antimicrob Agents Chemother 2000 Feb;44(2):447-9
In vitro activity of ABT-773, a new ketolide, against recent clinical isolates of Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis.
Brueggemann AB, Doern GV, Huynh HK, Wingert EM, Rhomberg PR
Medical Microbiology Division, Department of Pathology, University of Iowa College of Medicine, Iowa City, Iowa 52242, USA.
(*Also a possible interview candidate*)
The in vitro activity of ABT-773 was evaluated against Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis isolates. ABT-773 was the most active antimicrobial tested against S. pneumoniae. ABT-773 and azithromycin were equivalent in activity against H. influenzae and M. catarrhalis and more active than either clarithromycin or erythromycin. (*Again, good in vitro results for Abbott*)
PMID: 10639382, UI: 20107001

02831133 (THIS IS THE FULLTEXT)
Respiratory Tract Infections: Ketolides Comprise New Family of Antibiotics (Aventis' antibiotic Telithromycin shows in vitro activity against pathogens that lead to community- acquired respiratory tract infections, according to PROTEKT study) TB & Outbreaks Week, p N/A June 13, 2000
DOCUMENT TYPE: Newsletter (United States)
LANGUAGE: English RECORD TYPE: Fulltext
WORD COUNT: 641
ABSTRACT:
Preliminary data reported from PROTEKT (Prospective Resistant Organism Tracking for the Ketolide Telithromycin), a global study involving 66 laboratories, has found that telithromycin

has demonstrated in vitro activity against pathogens that lead to community- acquired respiratory tract infections (RTIs) (*This study involves only the Aventis antibiotic, and is sponsored by Aventis)* Telithromycin is part of new family of antibiotics known as ketolides, being explored as RTIs grow increasingly resistant to commonly used antibiotics. Globally, RTIs kill more than 50 mil people yearly. PROTEKT is sponsored by Aventis Pharma. Ketek (telithromycin) was submitted by Aventis Pharmaceuticals to the US Food and Drug Administration (FDA) and the European Agency for the Evaluation of Medicinal Products for marketing approval earlier in 2000. Full text further discusses the PROTEKT study.

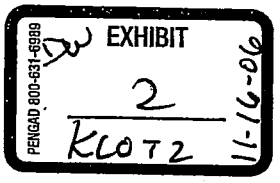
PLs' KS

From: Lynn C. Klotz [LynnKlotz@compuserve.com]
Sent: Friday, June 02, 2000 10:06 AM
To: Blewitt, Stephen
Subject: my cv and thoughts about strategy

Attached is my cv, in case you haven't seen it before.

Also, your idea about financing baskets of drugs, and that combined with options to convert to stock targeted to companies of sufficient size and in need of mezzanine or post-mezzanince financing seems like the base of a good strategy to me. We should discuss why or why not some active strategy like this one can be pursued.

-- Lynn



CURRICULUM VITAE

Lynn Charles Klotz

Mailing Address:
71 Winslow Avenue
Somerville MA 02144
Tel: 617-623-6375
Fax: 617-623-6372
E-mail: lynnklotz@compuserve.com

Selected Professional Experience:

- Member of four-person team consulting with the President and Senior Administration of Mississippi State University to provide a strategic plan for their Life Sciences Institute, June 1999-March 2000.
- Professor and Course Director, Harvard University Summer Executive Program, for the course "Biotechnology and Modern Drug Discovery and Development," July 1997, 1998
- Special Consultant in Technical Strategy to Codon, Inc. and Oncor, Inc., 1992 - 1998
- Chair, Subgroup on Industry Concerns, Federation of American Scientists Working Group on Biological Weapons Verification
- Member, Founding Team and Scientific Advisory Board, Codon, Inc. 1994 - 1998.
- Member, "BWC Industry Working Group," Belfer Center for Science and International Affairs, Kennedy School of Government, Harvard University, 1998.
- Member, "Biotechnology Research and Industry Working Group", Center for Science and International Affairs, Kennedy School of Government, Harvard University, 1991 - 1993.
- Special Consultant to Tufts University in Biotechnology, 1992 - 1993.
- Managing Partner, Devonshire Biotechnology Group, 1990 - 1992.
- Member Board of Directors, BioTechnica International, Inc., 1981 - 1989.
- Vice President New Business Development, BioTechnica International, Inc., 1986 - 1987.
- Vice Chairman Board of Directors, BioTechnica Diagnostics, 1985 - 1987.
- Vice President Scientific Planning, BioTechnica International, Inc., 1983 - 1986.
- Vice President Scientific Operations, BioTechnica International, Inc., 1981 - 1983.
- Lecturer at the Rank of Associate Professor, Biochemical Sciences, Princeton University, 1979 - 1981.
- Associate Professor, Biochemistry and Molecular Biology, Harvard University, 1975 - 1979.
- Assistant Professor, Biochemistry and Molecular Biology, Harvard University, 1971 - 1975.

Examples of Recent Biotechnology-related Activities

- Developed strategic plan and devised program area for the life-scieicnes effort for a major land-grant university;
- Evaluated for a major investment bank a company's technology, competititors technology, intellectual property and regulatory aspects of products;
- Determined the likely status in the year 2005 of drug discovery and development in a major therapeutic area for a major investment bank;
- Invented, wrote a patent application, carried out a market assessment, and devised a business strategy for a number of agricultural and industrial applications for an array of *in vivo* directed gene mutation methods;
- Carried out a complete analysis of a company's and competitors' intellectual property position;
- Wrote business plans for first and second-stage financing;
- Carried out a formal screening process to decide which of many clinical applications should be pursued for a family of novel small-molecule drugs;
- Conducted a pharmacoeconomic analysis of genetic risk testing; and
- Identified a science/business opportunity from a university's basic research in infectious disease and wrote a strategic plan to exploit the opportunity.
- Helped assemble scientific advisory boards for a startup;
- Wrote first drafts of several patents, some of which were my own inventions;
- Wrote grants that have been awarded; and
- Carried out a mathematical pharmacokinetic analysis of a large-molecule drug-delivery method to justify its development.

Recent Biotechnology-related Presentations:

Speaker "Pharmacoeconomic Consequences of Genetic Risk Assessment for Hereditary Breast Cancer," at conference: New Approaches in Diagnosing and Treating Breast Cancer, sponsored by Cambridge Healthtech Institute, Philadelphia PA, November 1994.

Speaker "Pharmacokinetics and Pharmacoeconomics in Drug Development," at Conference: Pharmacokinetic Analysis sponsored by Cambridge Healthtech Institute, Washington DC, October 1994.

Panel member and speaker, "The Biotechnology Industry" at conference: Technology and Employment, sponsored by MIT, Cambridge MA, January 1994.

Chairperson, organizer, and Keynote Speaker, "Biostrategies" Conference, Presented by the Wang Institute of Boston University. Tyngsboro, Ma., November 1990.

Recent Biological-Weapons-Treaty-Related-Presentations:

Speaker and panel-discussion moderator for a U.S. Congressional Briefing "The Shape of a Compliance Regime for the Biological Weapons Convention," Washington DC, February 1999.

Speaker "Challenge Investigation Voting Procedures for a BWC Compliance Regime: The Effect of Abstentions," at Conference: Association of Politics and the Life Sciences, Boston MA, September 1998.

Speaker "Meeting U.S. Industry Concerns within a Strong BTWC Compliance Regime," at Conference: A Strengthened Biological and Toxin Weapons Convention, Vienna Austria, 1998.

Speaker "Evasion Scenarios and Countermeasures," at Workshop: The Utility of Sampling and Analysis for Compliance Monitoring of the Biological Weapons Convention, Washington DC, October, 1996.

Speaker "FAS and US Industry Recent Discussions," at FORUM: Triggers for Declarations and Inspections/Visits in a BWC Compliance Regime and Incorporation of Export Controls in the Regime, Palais des Nations, Geneva Switzerland, July 1996

Education:

University of California, San Diego. 1966-1971. Ph.D. in Chemistry.
Advisor: Professor Bruno Zimm

Princeton University. 1962-1965. B.A. in Mathematics.

Trenton Junior College Evening Division. 1958-1962.

Outstanding Honors:

Camille and Henry Dreyfus Foundation, Teacher-Scholar Grant, 1975. Single harvard University nominee. At the time, this grant was awarded each year to only six individuals in the U.S.

Research Publications:

Published over 40 research papers and review articles in leading scientific and business journals and awarded two U.S. patents. Ten publications or issued papers on Biological Weapons Control.

Books Published:

Edward J. Sylvester and Lynn C. Klotz, "The Gene Age: Genetic Engineering and the Next Industrial Revolution." Charles Scribner's Sons, New York.

First Edition: 1983, Nominated for Pulitzer Prize by the publisher. Second Edition: 1987.

References

Business:

Dr. Jay George, Assistant Director, Program Technology Development, National Cancer Institute. Bldg. 31, Room 11A03, 31 Center Drive, MSC 2590, Bethesda, MD. 20892-2590. Tel: 301-435-3877. Dr. George was formerly Vice President of Research for Oncor, Inc. and Codon, Inc.

Dr. Ralph Hardy, President, National Agricultural Biotechnology Council. Summer address: 31 Oak Street, Fenelon Falls, Ontario, Canada K0M1N0, summer tel: 705-887-9887, other tel: 607-254-1240. Dr. Hardy was formerly Director of Life Sciences at DuPont, President and Chief Operating Officer at BioTechnica International, and President of the Boyce Thompson Institutute at Cornell University.

Mr. Charles Morris, Devonshire Partners, 100 W. 57th Street Apartment No. 17I, New York NY 10019. Tel: 212-489-9802. Mr. Morris was formerly Group Executive, Chase Manhattan Bank.

Dr. David Bing, Scientific Director of DNA Repository, Genomics Collaborative, 99 Erie Street, Cambridge, MA 02139. Tel: 617-661-2400. Dr. Bing was formerly Vice President, The Center for Blood Research, Inc.

Dr. Sandy Primrose, Chief Operating Officer, Azur Environmental, Ltd., 540-545 Eskdale Road, Winnersh Triangle, Wokingham, Berkshire RGG41 5TU UK. Tel: 011-44-118-927-7000. Dr. Primrose was formerly General Manager of Life Sciences at Amersham International; and Senior Director of Drug Development at Searle.

Academic Science and International Affairs

Professor Jacques R. Fresco, Department of Molecular Biology, Lewis Thomas Laboratory, Princeton University, Princeton NJ 08544: 609-258-3927

Professor Paul Doty, Director Emeritus, Center for Science and International Affairs, John F. Kennedy School of Government and Professor Emeritus, Biochemistry and Molecular Biology, Harvard University, Cambridge MA 02138: 617-495-1404

Dr. Barbara Rosenberg, Chair, Federation of American Scientists Working Goup on Biological Weapons, 307 Massachusetts Avenue NE, Washington DC 20002. Tel: 914-251-6643

Professor Bruno H. Zimm, Department of Chemistry, University of California at San Diego, La Jolla California 92093: 619-534-4416

Professor Thomas M. Roberts, Dana Farber Cancer Institute, 44 Binney Street, Boston MA 02115. Tel: 617-632-3049

Publications:

I. Science publications

Fresco, J.R., Klotz, L.C., and Richards, E.G., (1963). A New Spectroscopic Approach to the Determination of Helical Secondary Structure in Ribonucleic Acids. Cold Spring Harbor Symp. Quant. Biol., 28, 83-90.

Massoulié, J., Blake, R., Klotz, L.C., and Fresco, J.R., (1964). Une Méthode Spectrophotométrique Permettant d'Etudier Séparément les Complexes en Double et Triple Hélice Formés par les Acides Polyriboadénylique et Poly-ribouridylique. C. R. Acad. Sc. Paris, 259, 3104-3107.

Massoulié, J., Guschlbauer, W., Klotz, L.C., and Fresco J.R., (1965). Etude des Complexes Formés par les Acides Poly-adénylique et Polyuridylique. Caractérisation des Complexes par les Spectres Différences. C. R. Acad. Sc. Paris, 260, 1285-1288.

Blake, R.D., Klotz, L.C., and Fresco, J.R., (1968). Temperature Dependence of Kinetics of Complex Formation in Equimolar Mixtures of Polyriboadenylate and Poly-ribouridylate. J. Amer. Chem. Soc., 90, 3556-3562.

Klotz, L.C., (1969). Dependence of Polynucleotide Helix-Coil Transition Theory on the Ring Closure Exponent. Biopolymers, 7, 265-273.

Chapman, R.E., Jr., Klotz, L.C., Thompson, D.S., and Zimm, B.H., (1969). An Instrument for Measuring Retardation Times of Deoxyribonucleic Acid Solutions. Macromolecules, 2, 637-643.

Holdy, K.E., Klotz, L.C., and Wilson, K.R., (1969). Molecular Dynamics of Photodissociation: Quasidiatomic Model for ICN. J. Chem. Phys., 52, 4588-4599.

Klotz, L.C., (1971). Viscosity and Retardation-Time of the DNA in Cell Lysates of B. subtilis and E. coli. Ph.D. Thesis, University of California at San Diego. Prof. Bruno H. Zimm, Thesis advisor.

Klotz, L.C. and Zimm, B.H., (1972). Size of DNA Determined by Viscoelastic Measurements: Results on Bacteriophages, Bacillus subtilis and Escherichia coli. J. Mol. Biol., 72, 779-800.

Klotz, L.C. and Zimm, B.H. (1972). Retardation Times of Deoxyribonucleic Acid Solutions. II. Improvements in Apparatus and Theory. Macromolecules, 5, 471-481.

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Kavenoff, R., Klotz L.C., and Zimm, B.H., (1973). On the Nature of Chromosome-sized DNA Molecules. Cold Spring Harbor Symp. Quant. Biol., 38, 1-8.

Roberts, T.M., Tuttle, R.C., Allen, J.R., Loeblich, A.R. III, and Klotz, L.C., (1974). New Genetic and Physiochemical Data on Structure of Dinoflagellate Chromosomes. Nature, 248, 446-447.

Rau, D.C. and Klotz, L.C., (1975). A More Complete Kinetic Theory of DNA Renaturation. J. Chem. Phys., 62, 2354-2365.

Lauer, G.D. and Klotz, L.C., (1975). Determination of the Molecular Weight of Saccharomyces cerevisiae Nuclear DNA. J. Mol. Biol., 95, 309-326.

Allen J.R., Roberts T.M., Loeblich, A.R. III, and Klotz, L.C., (1975). Characterization of the DNA from the Dinoflagellate Crypthecodinium cohnii and Implications forNuclear Organization. Cell, 6, 161.

Muller, W.A., and Klotz, L.C., (1975). Retardation Time Measurements on Replicating Bacillus subtilis Chromosomes: Effect of EDTA Concentration. Biochim. Biophys. Acta, 378, 171-185.

Roberts, T.M., Lauer, G.D., and Klotz, L.C., (1976). Physical Studies on DNA from "Primitive" Eukaryotes. CRC Critical Reviews in Biochem., 3, 359-449.

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Lauer, G.D., Roberts, T.M. and Klotz, L.C., (1977). Determination of the Nuclear DNA Content of Saccharomyces cerevisiae and Implications for the Organization of DNA in Yeast Chromosomes. J. Mol. Biol., 114, 507-526.

Rau, D.C. and Klotz, L.C., (1978). A Unified Theory of Nucleation-Rate-Limited DNA Renaturation Kinetics. Biophys. Chem., 8, 41-51.

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Mitchell, R.M., Loeblich, L.A., Klotz, L.C., and Loeblich, A.R. III, (1979). DNA Organization of Methanobacterium thermoautotrophicum. Science, 204, 1082-1084.

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Hinnebusch, A.G., Klotz, L.C., Immergut, E., and Loeblich, A.R. III, (1980). Deoxyribonucleic Acid Sequence Organization in the Genome of the Dinoflagellate Crypthecodinium cohnii. Biochemistry, 19, 1744-1755.

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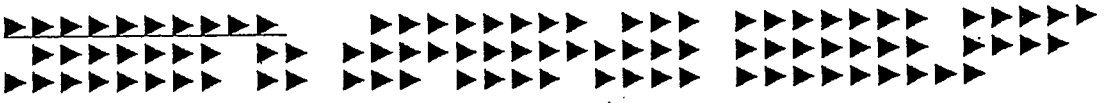
French, C.K., Simon, S.L., Chen, M.C., Eklund, S.M., Klotz, L.C., Vaccaro, K.K., and Savitt, E.D., (1989). DNA Probe Diagnosis of Periodontal Disease. Edited by Swaminathan, B., Prakash, G., and Dekker, M.. Nucleic Acid and Monoclonal Antibody Probes; Applications in Diagnostic Microbiology.

II. Issued patents

U.S. Patent 4,866,167. Issued on September 12, 1989. "Detection of Human Oral Cells by Nucleic Acid Hybridization." Inventors: Michael C. Chen, Pearl M. Chen and Lynn C. Klotz.

U.S. Patent 4,925,785. Issued May 15, 1990. "Nucleic Acid Hybridization Assays." Inventors: Chang-Ning J. Wang and Lynn C. Klotz.

III. Submitted patents and patents in preparation



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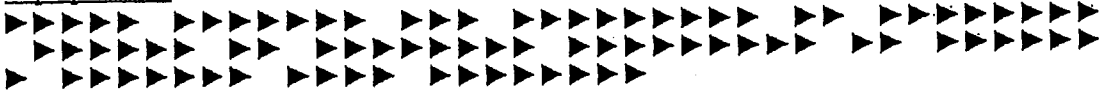

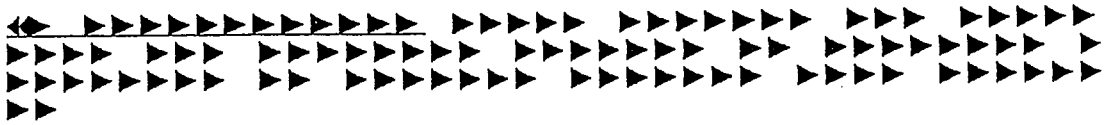

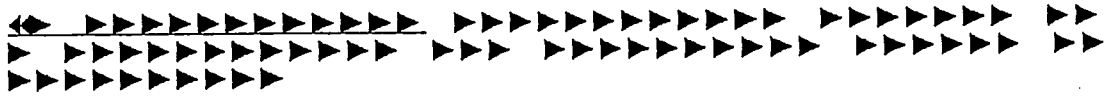

IV. Business Articles

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Klotz, L.C., "Biotech's Future in Bay State." Boston Business Journal, March 26-April 1, 1984.

Kerr, A.P., Klotz, L.C. Morris, C.R. and Schatz, R.W., "A Paradigm for Analyzing Biotechnology Investing and Partnering Opportunities." BioPharm, June 1991.

Kerr, A.P., Klotz, L.C., Morris, C.R. and Schatz, R.W., "An Early Warning Tool for Pharmaceutical Development." BioPharm, Vol. 5, No. 2, February 1992.

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and Development Strategies: A Look at Six Leading Biotechnology Companies." DR Reports, Decision Resources, Waltham MA.

Branca, A.F. and Klotz, L.C. (1993). "Transdermal Patches: The Forces Driving an Expanding Market", Spectrum Series, Decision Resources, Waltham MA

Klotz, L.C. and Allison M. (1994). "Rational Design of Small Molecule Therapeutics: Assessing Computer-Based Drug Discovery," Therapy Markets and Emerging Technology Series, Decision Resources, Waltham MA.

Sylvester, E.J. and Klotz, L.C. (2000). "Will the 21 st Run on Green or Black Gold?" USA Today, February 1, 2000, p. 15A

V. Biological weapons control publications

Klotz, L.C.--principal author (1995), "Potential for New Approaches to Microorganism Identification," Working Paper, Federation of American Scientists Working Group on Biological and Toxin Weapons Verification.

Klotz, L.C. and Rosenberg, B.H. (1996), "Sampling and Analysis of Proprietary Microorganisms while Protecting Confidential Proprietary Information," Working Paper, Federation of American Scientists Working Group on Biological and Toxin Weapons Verification.

Ambassador J. Leonard, W. Carpenter, B.H. Rosenberg and L.C. Klotz (1996), "Strengthening the Biological Weapons Convention: the Impact on Confidential Proprietary Information and Property," Working Paper, Federation of American Scientists Working Group on Biological and Toxin Weapons Verification.

Klotz, L. C. (1997), "Evasion Scenarios and Countermeasures," in The Utility of Sampling and Analysis for Compliance Monitoring of the Biological Weapons Convention," Monterey Institute for International Studies, Monterey CA, February 1997.

Klotz, L. C. (1997)--principal author "Confidentiality Can Be Protected During Sampling and Analysis in a BWC Compliance Regime," Federation of American Scientists, Working Paper, Federation of American Scientists Working Group on Biological and Toxin Weapons Verification.

Klotz, L. C. and Rosenberg, B.H. (1997), "Rapid Resolution of Questions that Might Arise During Nonchallenge Visits," Working Paper, Federation of American Scientists Working Group on Biological and Toxin Weapons Verification.

Rosenberg, B.H and Klotz, L. C.--contributor (1997), "Making Random Non-Challenge Visits Friendly," Working Paper, Federation of American Scientists Working Group on Biological and Toxin Weapons Verification.

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PLs' KU

From: Lynn C. Klotz [LynnKlotz@compuserve.com]
Sent: Tuesday, June 20, 2000 6:46 PM
To: Blewitt, Stephen
Subject: Preliminary Abbott basket analysis

It took me less time than I thought to consolidate my notes, so here it is in the attachment. I will not do any more work, until we agree on next steps. I am a little under two days work so far.

– Lynn

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(prepared by Lynn C. Klotz, PhD)

Preliminary Analysis of Abbott Drug Basket

file: abbott-bask

General Thoughts, Ideas and Questions

The basket is really two baskets

Some of the drugs in the basket are well along in clinical trials and represent new but more traditional approaches to diseases. In contrast, the remaining drugs are cytostatic cancer agents for cancer, and since this is a new untried strategy for everyone, it is high risk. The risk is compounded by the fact that most are in discovery, not in clinical trials.

In our analysis, we should perhaps treat the basket as two, and come up with independent courses of action for each. The traditional drugs in the basket cover a wide range of diseases and thus reduce the risk of competitor's drugs totally shutting Abbott out.

Some thoughts on cytostatic drugs

There is a general clinical trials issue for cytostatic drugs: Many will enter trials in combination with conventional cytotoxic drugs and effective combinations will have to be determined empirically. Intermediate and surrogate measures of biological response will have to be developed. Regulatory agencies are grappling with the same issues.

The idea of using cytostatic drugs in combination with traditional drugs is however enormously appealing.

Do cytostatic agents reflect Abbott's major cutting-edge cancer strategy? If not, why are they being offered to Hancock?

Precisely what is Hancock buying?

In the areas where Abbott is still in discovery and doesn't have specific drug candidates will Hancock be buying royalty rights for all compounds, the first to enter clinical trials or the first to enter the marketplace. Rights to the first to enter the marketplace is greatly preferred, since it eliminates the risk that the drug will make it through trials. This is one way to deal with the cytostatic area where the candidates are not yet in clinical trials.

For some compounds, Abbott is conducting clinical trials for one indication, but they state that the compound has shown promise for other indications (off label or not) and diseases. It is

preferable that Hancock has royalty rights for the compound itself– that is all indications and diseases, rather than the first indication for which it is being tested in trials.

How do we value the technical aspects of the drug basket and competitive drugs?

First, we might search the business press and MedLine to validate Abbott's claims and analysis for each drug in the basket. Then, for some (many?) basket drugs we should seek the opinion of one to two experts. Literature searching one basket drug is likely a four to five hour task, and may be necessary preparation to prime us with goodquestions for the experts. We should not need more than two hours of an expert's time. From the point of view of due diligence, experts should be retained for most of the drugs.

How do we value sales of the drug basket?

Estimating actual sales of drugs in the basket is difficult, but is key for deciding on the amount of investment and royalty rate. Along with clinical trials, success risk it is the other main source of risk, assuming Abbott doesn't just disappear. Abbott's sales estimates are likely all high, because they would need to be optimistic to sell the drugs/programs internally. A few ideas for schemes for estimating sales are presented below:

1) In this scheme, determine the dollar sales for the top five (ten or twenty?) drugs in each therapeutic area (disease targets), and the average sales of all drugs in that disease area. This data is likely available for many of the disease targets–and Abbott presents some data. Then assume both: optimistically, sales will reach a level of the average of the top five; and conservatively sales will reach the average of all drugs in that area–to give us a feel for the range of sales. For example, cancer and antibiotic markets are highly fragmented, so the average sales of a particular drug is likely small, perhaps less than $100 million. The average sales of the top five drugs may also be less than $500 million, less than half of Abbott's projected sales. Of course, we must still take into account the average probabilities that the drugs not fail in clinical trials and reach the marketplace.

2) In this scheme, we try to estimate sales, and probabilities more from "first principles." Start with Abbott's sales estimates and adjust them downward based on market risk factors. The average probabilities that the drugs ever reach the marketplace must be separately taken into account, and should be adjusted upward or downward based on clinical trials risk factors.

The clinical trials risk factors are:

- uncertainties about the targets key role in the disease (would adjust downward the probability that the drug reaches the marketplace)
- uncertainties about toxicity (would adjust probability downward)

- easily defined or fuzzy clinical trial endpoints (would adjust probability upward or downward). For example, antibiotics have easy endpoints--the patient get better and no evidence of infection; cytostatic drugs have difficult to measure endpoints when in combination with traditional drugs.

We would adjust the development phase probabilities using factors ct_i which range from perhaps zero to above one. We would need to define the appropriate adjustment factors

The market risk factors are:

- number of competitors
- efficacy and side-effects of Abbott's drug vs. competitor's drugs
- cost of Abbott drug vs competitor's drugs
- market need, dire to modest

We would adjust downward Abbott's sales estimates using factors mr_i between zero and one.

Of course determining the ct_i and mr_i factors is somewhat guess work, but at the very least the effort would allow us to better focus on the issues and get some idea of value and risk of the package.

Thoughts on the investment risk spectrum:

- *Example of a zero risk approach:* If Hancock received a guaranteed return on its investment each year increasing yearly regardless of sales, so that the internal rate of return was significant (e.g., 15%), there would be no risk but also no upside reward. One way of receiving the return would be for it to start, for example, in 2003 and ramp up to a maximum in 2015 and decline over the next five years. Under this scenario, Abbott would be paying return from the anticipated drug sales, and Abbott would experience all the up-side and down-side. Hancock would have no risk.

- *Example of an intermediate risk approach*: Receive a guaranteed internal rate of return of for example 5% to 7% as in the above, and receive the rest of the return based on actual sales, so upside potential exists. In this model with a 7% return, one could perhaps even take Abbott's likely inflated sales estimates, since it is all upside above 7%. This removes much of the uncertainly of estimates of eventual sales.

- *Highest risk approach:* Hancock does its best to estimate what it expects for sales on the drug basket, makes the appropriate investment with an appropriate royalty rate, and receives all its return as royalty on actual sales.

An idea for simplifying the financial calculations of appropriate investment amount and royalty rate to give an acceptable internal rate of return (IRR) to Hancock.

Since all the drugs in the basket which are in clinical trials are about the same phase of clinical trials (this excludes all the cytostatic agents except one) begin sales approximately between 2003-2005 and ramp up to maximum sales in approximately 2010-2013, and patents expire about 5 years later, we could use the linear IRR model developed at present only for single drugs by treating the package as a single drug, with total sales and average probability.

This will be a quick and dirty way, and likely as good as a more detailed model, to get in the range of reasonable royalty return.

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Summary Profile of the Basket

Drug	Disease Targets	Mechanism of Action	Stage of Development	Preliminary Assessment Promise/ Market-risk	Projected Maximum Sales
ABT-980	benign prostatic hyperplasia (BPH)	alpha 1a adrenoceptor antagonist	phase II completed, phase III begun?	high/ medium	$700 mil. (worldwide)
ABT-627	cytostatic therapy for hormone resistant metastatic prostate cancer (PCA)	endothelin ET-1 antagonist for Eta receptor	phase II completed, phase III begun?	medium/ medium	$1,000 mil. (worldwide)
ABT-773	bacteria resistant to present antibiotics	new class of antibiotics (ketolides)	phase III?	high/ low	$1,000 mil. (worldwide)
ABT-594	diabetic neuropathic pain	cholinergic channel modulator (chCM)	phase IIa, Phase IIb about to begin	high/ medium	$1,100 mil. (worldwide)
A-254751	cytotoxic therapy for late stage breast, NSCL, ovarian, and pancreatic cancers	binds to the colchicine site on tubulin to inhibit microtubule formation	preclinical or phase I?	high/ high	$680 million (worldwide)
ABT-518	cytostatic therapy for late stage breast, NSCL, ovarian, and pancreatic cancers	matrix metallo proteinase inhibitor (MMP1)	preclinical or phase I	high/ high	$850 mil. (worldwide)
FTI	same as ABT-518	farnesyl-transferase inhibitors which block either farnesylation of RAS or RhoB	early preclinical?	high/ high	$850 mil. (worldwide)
Uro-kinase inhib-itors	same as ABT-518	serine protease inhibitor	early preclinical	high/ high	$850 mil. (worldwide)

Note to table: Market risk, in this preliminary assessment is a qualitiative "feel" based on uncertainties in technical strategy, uncertainties in clinical trials, perceived value of the drug compared to others, number of competitors.

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Issues, Questions, Evaluation Tasks

ABT-980 (alpha 1a adrenoceptor antagonist for BPH).

Product is scheduled to begin Phase III clinical trials in second quarter 2000. Has it begun Phase III? What were the results of Phase II?

According to Abbott, uroselective agents such as Tamsulosin (Flomax®) and ABT980 are predicted to be the standard of care replacing existing non-selective agents. We should search the literature for a confirmation of that statement, and understand the medical communities view of selective vs non-selective agents and competitor potential of Flomax.

At time of ABT980 launch, Abbott expects competition from several other alpha 1a blockers. Abbott lists three key competitive drugs in clinical trials, one lead competitor/drug is Yamanuchi/Glaxo's drug Dutasteride which is in Phase III trials. As a "spot check," we should learn what we can about the status and promise of that drug?

ABT 627 (endothelin ET-1 antagonist for Eta receptor for metastatic prostate cancer).

Abbott classifies this drug as a cytostatic agent not a cytotoxic agent, because it only retards progression of PCa and doesn't cure it. Abbott is positioning it as a drug that delays progression and improves quality of life for HRPCa patients. In clinical trials, quality of life is a somewhat fuzzy endpoint, but some measure can be achieved. Since prostate cancer usually progresses slowly, measuring a delay in progression may be difficult in clinical trials? What effect will this have on FDA's assessment?

Has the drug yet entered Phase III trials, if so when? Are preliminary data available? Is it the only Abbott cytostatic agent in advanced clinical trials?

The drug is in Phase I trials for other cancer types. Animal studies (Abbott's or general literature knowledge?) indicate that there is potential for other non-cancer conditions? Would Hancock receive royalties for these too; put another way, is Hancock buying royalty shares for all sales of the compound, or for just prostate cancer?

For advanced PCa, hormone therapy is the main treatment, but treatment becomes ineffective after two to three years with reduced life expectancy of only 12 months, and no chemotherapy has shown promise for these patients. Perhaps we should "spot-check" the accuracy of these statements. (Patients resistant to hormone therapy are called HRPCa.)

Novatrone (Novantrone/Immunex) is the only drug for HRPCa with pain. We should perhaps ascertain its promise as a competitor, as a "spot-check" on Abbott's reasoning.

Are there enough HRPCa patients to justify Abbott's $1 billion projected sales of the drug, especially since there are at least 10 competitive drugs in advanced clinical trials? How will PSA testing eventually reduce the number of patients with metastatic disease? I believe it has a great success in the US.

ABT-773 (a new class of antibiotics for bacteria resistant to present antibiotics)

We should MedLine and business database search ketolide antibiotics to independently determine their promise. Then an expert like Stuart Levy should be consulted. Andy Onderdonk might also be able to supply the names of experts for us.

Phase II clinical trial results look impressive to me: highly efficacious against four bacteria. Why did they pick those four bacteria? Since the multicenter phase II clinical trials were completed in April 1999 and the data have been analyzed, the drug should be in phase III. Is it? How far along?

Antibiotic clinical trials are relatively straight forward, the infection disappears and the patient gets better in short time.

Adventis' ketolide (telithromycin/Ketek) is ahead with an NDA filed 3/00. Has it been approved?
How does Abbott's ketolide compare?

ABT-594 (cholinergic channel modulator (chCM), initial indication is for diabetic neuropathic pain).

The drug, according to Abbott, is expected to be the first cholinergic channel modulator on the market. How promising is this approach compared to others? We should look at the phase IIa results.

There may be a problem with the therapeutic window. Phase I studies indicated a maximum tolerated dose of 150 ug/day for an oral formulation. Abbott says for capsules results "suggest that higher doses can be tolerated." How much higher? Phase IIa studies suggest "a trend towards analgesic effect at 75 ug bi daily (BID). Thus, the therapeutic window may only be slightly greater than one, and about 10% of patients at 75 ug BID had a number of uncomfortable side effects such as headaches, nausea, etc. There appears to be some risk of not passing phase II clinical trials. We should perhaps get an assessment from a pain clinical-trials expert.

While the initial indication is narrowly defined as diabetic neuropathic pain, the ultimate market is for neuropathic chronic pain in general. This is an underserved market accrding to Abbott.

Pregabalin/Park-Davis is in Phase III (for neuropathic pain?) and is expected to be introduced in 2001. GV 196771 Glaxo is in phase II for neuropathic and chronic pain. These appear to be serious competitors, we should learn what we can about them from the literature, and an expert assessment.

A-254751 (binds to the colchicine site on tubulin to inhibit microtubule formation, for MDR resistant tumors)

The drug "inhibits the *in vitro* polymerization of microtubules." Also inhibits a broad spectrum of tumor-derived human cell lines including those that are pacitaxel and doxorubicin resistant due to MDR and other phenotypes. This meets a important market need.

In animal synergic (definition?)and xenograft models, "A-254751 demonstrated impressive oral anti tumor activity."

In dogs, there have been adverse cardiovascular effects (caused by vasoconstriction?), that have not been observed in patients. Does this mean that Phase I trials are underway, completed?

Abbott states that it will thoroughly quantify the risk from vasoconstriction in humans caused by intermittent and repeated dosing of the drug. The drug may well present too big a risk to humans and not make it out of phase I. What is Abbott's current status and assessment of the drug?

There are seven competitive colchicine site ligands in development by competitors. Three have been abandoned in Phase I (not safe) and one in phase II (why?). Three are still actively being developed. This both highlights the safety risk and the promise. We need a cancer experts assessment of the safety and promise of the approach (either Peter Glazer or someone he recommends).

I am surprised that their maximum sales estimate is less than $1 billion, as drugs that are effective and can defeat MDR should find high usage in a total cytotoxic market of over $7 billion.

ABT-518 (matrix metallo proteinase inhibitor program, cytostatic therapy for late stage breast, NSCL (non-small cell lung cancer), ovarian, and pancreatic cancers)

The MMP enzymes are elevated in cncer and are associated with the ability of cancers to metastasize. Inhibitors of MMP's may suppress tumors by suppessing invasion of the cancer into the blood and they may also suppress angiogenesis. Since they don't attack the tumor cells themselves, they are called cytostatic agents and represent chronic therapy. These may be small

molecule competitors to EntreMed's (Folkman's lab) angiogenesis drugs.

Abbott states that there are more than 200 compounds in development for cytostatic targets.

This is a program targeting gelatinase A and gelatinase B, because Abbott claims these two MMP's are particularly important in tumor progression. We should see what the literature says about the promise of gelatinase targeting as opposed to other enzymes involved in invasion.

Would Hancock's rights extend to all MMP inhibitors developed in the program or be limited to ABT-518?

Therapeutic window of 20 in rats bodes will to the drug.

These agents have the advantage that they can be given in combination with current therapy, so the FDA may allow clinical trials on early-stage cancer patients which would expand potential market too. In addition, in my view, these add-on combination therapies have unusual promise- but are high market risk because they are new.

AB518 has been tested in animals with good pharmacokinetics and toxicology.

Abbott expects sales to begin in 2006 peaking in 2012. This means the whole clinical trial process will take about 6 years which is about right for trials today. Will this drug enter Phase I this year, so that the time schedule can be met?

FTI program (farnesyltransferase inhibitors which either block farnesylation of RAS or RhoB, cytostatic therapy for late stage breast, NSCL, ovarian, and pancreatic cancers)

These agents appear to inhibit angiogenesis, and so are cytostatic agents.

According to Abbott, "farnesyltransferase inhibitors have demonstrated impressive anti tumor activity in preclincal models with activity equivalent to or better than that achieved with conventional cytotoxic chemotherapy given at maximal tolerated dose."

This approach is validated by the fact that there are 12 competitor drugs in development, five in clinical trials. Abbott may be late in a crowded field. Janssen Pharmaceutica/R-11577 is in Phase III and Schering-Plough/Sch66336 is in Phase II. We should learn about the promise of these two drugs, both to assess the real promise of the approach and the potency of the competition.

While Abbott is not yet in clinical trials, has it picked a promising candidate?

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Urokinase inhibitor program (serine protease that activates plasminogen to plasmin which breaks down basement membrane and interstitial matrix, cytostatic therapy for late stage breast, NSCL, ovarian, and pancreatic cancers)

Urokinase breaks down basement membrane and interstitial matrix required for tumor growth and metastasis.

Abbott's urokinase program is more advanced than competitors (at least seven competitors in preclinicals) with potency 20 fold more than nearest competitor.

Again, the number of competitors developing urokinase inhibitors validates the approach.

PLs' KY

From: Lynn C. Klotz [LynnKlotz@compuserve.com]
Sent: Friday, July 28, 2000 10:55 AM
To: Blewitt, Stephen
Subject: Abbott interview writeup

See attached. Overall, most questions were answered satisfactorally--certainly no indication of any deception on Abbott"s part. Only one question needs following up, the patent question on ABT-594. Let's talk to see where we go from here, and to discuss the format of the final report.

-- Lynn

File: interview-abbott

Telephone Interview with Abbott, Conducted by L. Klotz (consultant) and S. Blewitt.

Representing Abbott:

John Leonard, Vice President of Development
Phil _____, Corporate Licensing
Steve Cohen, Controller

[Steve, do you have full names and formal titles for the Abbott participants?]

Almost all answers were provided by John Leonard, as the other two Abbott participants were not scientists and this was a technically oriented interview. Interviewer questions and comments are in italics, Abbotts response in normal type.

ABT-773, ketolide antibiotic for bacteria resistant to antibiotics

To attain a $1 billion market for a ketolide antibiotic as Aventis predicts (and you also predict), one of the experts we interviewed thought that two things must happen. It must unseat erythromycin, and it must out compete the new fluoroquinolones which are going after the same market. Do you agree with that assessment? If so, how do you see the marketing devlop for ABT-773?

Erythromycin was unnseated a decade ago, the erythromycin derivative zitromax has $600 to $700 US sales and over $1 billion worldwide. It has 15% market share [*of the deriviative market?*].
[He mentioned a few other big sellers, from which it might be concluded that there is a very big total market in which Abbott could achieve a significant market share.]

Fluoroquinolones in the past were used for urinary tract infections, but their marketers are trying to move into the respiratory infection market.

Ketolides are related to macrolides, for which several resistance mechanisms exist. Do you expect resistance to develop rapidly from some of the minor macrolide resistance mechanisms, even though ketolides have been designed to circumvent the major efflux and ribosomal methylation mechanisms?

In the US, efflux is the major mechanism of resistance. I believe in Japan the ribosomal mechanism may be important too. ABT-773 was originally designed and synthesized to avoid efflux. It has demonstrated efficacy on normally antibiotic resistant cells. We are about to enter Phase III trials.

One expert stated that ketolides have a limited range of bacterial-species activity, which will

probably limit their usefulness to respiratory infections. While respiratory infections (sinusitis, bronchitis and pneumonia) are a very large market, do your market estimates include other large markets? If so, why do you think ABT-773 can serve those other markets?

ABT-773 was designed first and foremost for respiratory indications.

Your Phase II clinical data indicates a 92% effectiveness (overall eradication) against H. Influenzae. How does this compare to erythromycin? If this indicates that ABT-773 is more effective than erythromycin against H. Influenzae, how do you see that affecting market size? Can you break down the increase in market for us.

Very early on we specifically designed our clinical trials to look at *H. Influenzae,* "which sets the bar" for these antibiotics. ABT-773 is as good or maybe better, but the study was small.

Do you see a competitive threat from the new peptide antibiotics such as Daptinomycin?

They are low on our radar screen, because they are IV administered. ABT-773 is for ambulatory patients, who have a cough, a stuffy nose. The IV administered antibiotics are for hospital use. We are developing an IV form of ABT-774, to compete in that market, but the market is small, and we haven't really talked too much about this.

ABT-594, cholinergic channel modulator for diabetic neuropathic pain

Experts in neuropathic pain point to pregabalin (Parke-Davis, Phase III trials) as being especially promising, because it works as well as gabapentin and is safe. How does ABT-924 stack up against pregabalin? Pregabalin will likely finish clinical trials and be approved (if it is approved) before ABT-924. Although measures have been developed, pain relief is subjective, so demonstrating to the FDA that ABT-594 is more efficacious than gabapentin may be difficult. Could the difficulty of providing convincing statistics prevent the approval of ABT-924?

We haven't compared the two drugs head-to-head, but from what we see in the pregablin literature, we believe our drug is good. I doubt that the FDA would use pregablin as a standard for approval. In the neuropathic pain area, there are no standards. The last drug was approved 40(?) years ago. We see no approval risk for ABT-594 from pregablin. Also ABT-594 works through a different mechanism. There is a great need for drugs in the neuropathic pain area.

From your descriptive memorandum, ABT-594 appears to have a therapeutic window of only two to three. Is this small therapeutic window acceptable? Has the FDA approved neuropathic pain relievers with such a low therapeutic window?

Aspirin has a therapeutic window of only ten. For ABT-594, maybe we will be able to get a theoretical window greater than five. When we give patients the upper-limit dose, the side effects aren't dangerous: headache, vomiting. These minor side effects appear to go away over time.

A Merck study claims that in rats "ABT-594 did not cause rotarod impairment at antinociceptive doses but did cause hypothermia and life-threatening adverse effects including seizures." This study also says its results suggest "ABT-594 has nicotine-like dependence liability....These findings indicate that the acute safety profile of ABT-594 is not significantly improved over other nicotinic analgesics." Also, Novartis finds in rats that "ABT-594 dose-dependently increased tail flick latencies but only at doses that also disrupted performance in the rotarod test" Novartis also claims "In all tests, (+)-epibatidine was significantly more potent than ABT-594." According to Abbott, ABT-594 is as efficacious as (+)-epibatidine, which is too toxic for use . How do you explain the differences between your findings in rodents and humans and the Merck and Novartis findings in rodents?

Someone called my attention to the Merck study, I don't think I've seen the Novartis one. However, in clinical studies I would trade five million rats for a hundred people.

Why are Merck and Novartis taking "pot shots" at you?

I think Merck and Novartis are using us as a standard. We are the only drug to compare with. Merck bought Sybia, the company which has rights to many of the receptors like the one we are targeting.

Is ABT-594 clear of the Sybia's patents?

ABT-594 was prior to the Sybia/Merck arrangement. Future products must avoid Sybia's rights.

[*Note: this did not actually answer whether Abbott has an invention prior to Sybia, or if Sybia's patents may cover the receptor for Abbott's drug. We should clarify this.*]

In an Abbott year 2000 study in rats, ABT-627 (the advanced prostate cancer cytostatic and pain drug) was examined for diabetic neuropathy. How does the promise of ABT-627 compare to ABT-594 for neuropathic pain? Are the two drugs structurally related? Is Abbott heading toward clinical trials with ABT-627 for neuropathic pain?

Yes, we have looked at ABT-627 as an analgesic, it has limited value for pain, so we won't pursue it.

ABT-627 also might be used to treat cardiovascular disease. We don't serve that market, so we won't pursue that indication for business reasons.

<u>ABT-980, alpha 1a adrenoceptor antagonist for BPH</u>

In a Chinese literature study comparing selective (tamsulosin, Flomax) and non-selective (terazosin) alpha 1-adrenoceptor antagonists, tamsulosin showed better results in maximum urinary flow rate (Qmax), and average urinary flow rate (AFR). But the results, in our naive opinion, were not dramatically different. For example, AFR increased 37.5% for tamsulosin and

25.8% for Flomax. I know these drugs sell well, but I am not sure why.
In our human trials we look at flow, and we look at symptoms. Treating the symptoms is important. For example does the bladder empty completely, is urgency to urinate reduced or eliminated.

We have completed Phase II, clinical trials and are about to enter Phase III. Our data so far, show that ABT-980 is virtually super imposable on Flomax, maybe we are slightly better in a few areas.

At what point does the FDA say, OK we have a number of products on the market which are not improvements over the previous ones, we won't approve the next one because patients don't need another similar product?

This is an incremental product, a lot of what our industry does is incremental products. So it becomes a marketing and pricing issue. The FDA doesn't make decisions based on the number of products already on the market. In Europe, where prices are controlled, if a product is a me-too product, it can enter the market but at a lower price.

One literature study refers to a patient population that is responsive to alpha1-adrenoceptor antagonists. Does this mean there is a subgroup of patients that don't respond to BPH drugs targeted to alpha1-adrenoceptor? How big is this subgroup?

I can't answer that; on one has carried out pharmacogenetic studies. The subgroup referred to could be those whose prostate is so big, nothing short of surgery will help them.

A-254751, tubulin colchicine-site binding drug to inhibit microtubule formation for advanced cancers

One expert said, of the number of colchicine-site binding agents in preclinical and in clinical trials, combretastatin-A4 (Oxigene, Phase I trails) stands out. He said it is receiving a lot of attention because it is also an antivascular agent. How does A-254751 stack up against combrestatin?

I don't know.

A strikingly large number of colchicine-site drugs have been abandoned in clinical trials. One expert claims the older colchicine-binding drugs failed before they are too toxic. More specifically, the older drugs failed for pharmacokinetic reasons: mainly too long half-lives in the body. He further stated: what one wants are colchicine-binding drugs that get into cells quickly, do their job, and are eliminated from the body quickly. Do you agree with this assessment? What are the pharmacokinetics of A-254751? How does the drug escape MDR?

I can't give you the pharmacokinetic data from memory.

Could we look at it?
Yes, I can get it for you.

[*Since A-254751 is in early stage clinical trials, the data may give us some insight about its prospects. But I am already rating this drug as only having a fair chance of FDA approval based on the fate of the other colchicine-site binding agents. I don't see that the data can change that opinion, so I withdrew the request to see it.*]

We don't know how the drug escapes the MDR mechanism.

How does A-254751 compare to other colchicine-site binding agents regarding toxicity?

We think the window is pretty good compared to others.

Cytostatic drugs (except for ABT-627, the endothelin ET-1 antagonist)

One literature review indicated that approximately thirty angiostatic agents are undergoing clinical trials, with another fifty agents in preclinical testing. This is a crowded field. While Abbott's approaches are clearly competitive, how can Abbott achieve a large market share given the large number of competitors in the cytostatic area in general?

I agree that for cytostatic drugs in general their may be 50 to 200 in testing. To get the market lead, get one that works. In this business, there are a number of people who start things, many more than the ones who finish.

One expert tells us that so far the FDA has not wavered from the strict position of improved survival as the criterion for cancer drug approval. This would include longer survival and improved quality of life. They have not yet approved any drug for slower disease progression. Since cytostatic therapies don't kill tumor cells, the use of time to progression of disease seems to be the necessary clinical trials measure. What are the problems with this measure? Do you think the difficulty of measuring time to progression, lack of statistically significant evidence of longer survival, and difficulty in determining improved quality-of-life will prolong clinical trails or cause some drugs to fail to get FDA approval? How serious an issue is this?

You set this question up too starkly. Clearly drugs that make people to live longer, as long as they maintain a quality of life, are likely to be approved. With ABT-627, we are working with the FDA to determine what is a meaningful clinical progression. We are working with the FDA every step of the way.

For any of your cytostatic drugs, have you any data for cost utility = (long-term-cost)/(quality-life-years-saved)? In particular, if there are side-effects, quality-life-years saved may be much less than simply life-years-saved, and cost-utility may be high.

We haven't done cost-utility precisely, but we compare favorably with other products–for

example, ABT-627 compares favorably with Luprolide, a chemical castration drug with sales of $800 million. Also, Luprolide is very expensive.

In this regard, metalloproteinase inhibitors are particularly worrisome. One of our experts stated that the metalloproteinase inhibitor BB-94 has "underwhelming" efficacy. It is toxic and causes joint problems. Additionally, one literature study finds that the metalloproteinase inhibitor Marimastat had no survival advantage when compared to chemotherapy with gemcitabine in advanced pancreatic cancer, and Abbott states that Marimastat has dose-limiting joint side-effects. To play devil's advocate, you could argue: Why should the FDA approve a drug that does not prolong a patient's life and at the same time inflicts pain? Could failure for approval of Marimastat make the approval barriers higher for follow-on drugs? What evidence do you have that gelatinase inhibitors like ABT-518 might not have the same FDA approval concerns?

British Biotech was first with Marimastat, so it has the problems of being first. One thing Abbott has learned from Marimastat is that it is not selective enough. Abbott's metalloproteinase inhibitor avoids blocking a particular enzyme that is needed to keep joints clear. Abbott's drug does not create what we call "frozen shoulder." There is a good animal model that we use for frozen shoulder.

ABT-627, the endothelin ET-1 antagonist

Abbott's internal memorandum describes ABT-627 as a potent vasoconstrictor. Abbott indicated in its internal memorandum that the mechanism of action in prostate cancer wasn't yet known. Additionally, one of our experts said that reducing blood supply to tumor cells was likely not the mechanism by which ABT-627 delays prostate cancer progression, since the cancer metastasize to bone and is slow growing both indicating there is less need for a good blood supply. What are your latest thoughts about mechanism of action? A competitor who has a better knowledge of mechanism may be in good position to develop a superior drug.

Yes, we agree that the mechanism of action for metastacized prostate cancer is not vasoconstriction. We do have knowledge about mechanism for prostate cancer.

[*The interview ended here because Steve Cohen had an important meeting to attend. There was little need for additional questions on ABT-627 as well.*]

PLs' RR

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To: Stephen Blewitt
Dana Donovan

Fax: 617-572-1628
Tel: 617-572-9624

Date: May 6, 1999

Included in this fax is a draft of a general consulting agreement, just to have something in place when a consulting project comes up. The confidentiality agreement may be what you want since it is from our last contract. If not, e-mail me changes and I will incorporate them.

Regarding my rates, for longer projects I am certainly willing to negotiate lower rates, or as we did in the cancer project, negotiate a set total project cost.

CONSULTING AGREEMENT

This is an agreement, effective as of May 20, 1999, between Lynn C. Klotz an individual residing at 71 Winslow Avenue, Somerville MA 02144 ("the Consultant") and John Hancock Mutual Life Insurance Company, A Massachusetts Corporation ("Hancock").

Background

Under the terms set forth below, Hancock desires from time to time to retain the services of the Consultant to carry out consulting services, and the Consultant is willing to render such services.

Terms

1. The Consultant agrees that consistent with his other obligations to render to Hancock the services. All such services shall be rendered by the Consultant or by personnel selected by the Consultant who are bound by confidentiality agreement with the Consultant substantially similar to the Confidentiality Agreement between the Consultant and Hancock. The Consultant agrees to make all reasonable efforts to carry out the services.

2. Hancock agrees to pay the Consultant for the services at a rate of $200 per hour plus out of pocket expenses and expenses for assistants*, which shall be payable within four weeks from receipt of an invoice from the Consultant after completion of the consulting services. The Consultant and Hancock may negotiate other financial arrangements on a project by project basis.

* Out of pocket expenses shall not exceed $1,000 or 20% of the total consulting fee, whichever is greater, for the services unless otherwise agreed by Hancock.

3. The Consultant shall act as an independent contractor and not as an agent of Hancock and the Consultant shall make no representation as an agent of Hancock. The Consultant shall have no authority to bind Hancock or incur other obligations on behalf of Hancock.

4. In the event Hancock discloses information to the Consultant that it considers to be secret or proprietary ("Proprietary Information"), the Consultant agrees to maintain the Proprietary Information in confidence in accordance with the Confidentiality Agreement and to treat the Proprietary Information with at least the same degree of care and safeguards that he takes with his own proprietary information. Proprietary Information shall be used by the Consultant only in connection with services rendered under this Agreement.

Proprietary Information shall not be deemed to include information that:

(a) is in or becomes in the public domain without violation of this Agreement by the Consultant; or

(b) is already in the possession of Consultant, as evidenced by written documents, prior to the disclosure thereof by Hancock; or

(c) is rightfully received from a third entity having no obligation to Hancock and without violation of this Agreement by the Consultant.

5. The Consultant warrants that he is under no obligation to any other entity that in any way is in conflict with this Agreement and that he is free to enter into this Agreement.

6. This Agreement may be terminated by Hancock at any time before completion of the services ("early termination"). Notification of termination shall be delivered by certified letter or by fax to the Consultant. In the event that Hancock terminates this Agreement, the Consultant will be reimbursed by Hancock at the rate of $200 per hour for services already rendered under this Agreement. Reimbursement for expenses for assistants and out-of-pocket expenses will also be reimbursed by Hancock.

7. The Confidentiality Agreement will survive any termination of this Agreement for a period of three years after such termination.

8. This Agreement is not assignable by either party without the consent of the other.

John Hancock Mutual Life Insurance Company

By:_____

Title:_____

_____
Lynn C. Klotz